East of England Neonatal Neuroprotection Guideline

Diagnosis & Management of Neonatal Seizures in the Term Infant

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Approved by:

<table>
<thead>
<tr>
<th>Neonatal Clinical Oversight Group</th>
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<tr>
<td>Clinical Lead Mark Dyke</td>
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[Signature]
Diagnosis & Management of Neonatal Seizures

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1. INTRODUCTION

Evidence suggests neonatal seizures can be harmful to the developing brain of a baby, and anticonvulsants also have potential harmful effects on the developing brain. In the medical literature:

- There is uncertainty around when to treat seizures and how to assess the adequacy of treatment.
- There is insufficient evidence to support the use of any particular anticonvulsant over another, leading to inconsistent anticonvulsant practice.
- Due to the above reasons, there is no universally accepted evidence based guideline on neonatal seizures.

This guideline is based on clinical consensus across the East of England and expert opinion derived from textbooks and current medical literature.

2. BACKGROUND

- Seizures occur more often during the neonatal period than at any other time during life\(^1\).
- Seizures in the developing brain are poorly classified, frequently under diagnosed, difficult to treat and associated with poor neurodevelopmental outcome\(^2,3\).
- The incidence of seizures is estimated at 1.5-3.5/1000 term live births and 10-130/1000 preterm live births\(^4\). About 2000 cases of neonatal seizures are predicted in the UK each year.
- In term infants, the most common causes of seizures are hypoxic-ischaemic encephalopathy (HIE), ischaemic stroke and intracranial haemorrhage\(^5\); in extremely preterm infants, the most common cause is intracranial haemorrhage, and the presence of seizures is associated with adverse outcome\(^6,7\).
- Seizures in the developing brain have been shown to be an independent risk factor for adverse neurodevelopmental outcome\(^8,9\).
- The current best practice is to attempt to recognize seizures early, consider anticonvulsant therapy and monitor the effects of treatment. There is evidence that some anticonvulsant medication, while reducing the abnormal movements, does not reduce the electrical discharge\(^10\) (electro-clinical dissociation – see below).
- There is wide variation in clinical practice in both diagnosis and treatment of such seizures and this reflects the lack of clear evidence of the relative benefit and harm of the anticonvulsants. Further research is warranted into the efficacy and safety of different anticonvulsant medications.
2. DEFINITION

A seizure is defined as a stereotypic, paroxysmal spell of altered neurological function (behavioural, motor and/or autonomic function), due to abnormal electrical activity in the brain\(^1\). Historically, most neonatal seizures were identified by direct clinical observation. More recently, many neonatal intensive care units place increased emphasis on EEG monitoring to identify seizures. This monitoring can include principally, conventional EEG, or amplitude-integrated EEG (aEEG), or both. An expanded role for EEG monitoring has been advocated by the 2011 WHO guideline\(^11\).

3. AETIOLOGY

Neonatal seizures are a clinical and/or electrical manifestation of an underlying pathology. The most common causes are listed in table 1 below.

<table>
<thead>
<tr>
<th>Table 1 Contribution of causes of neonatal seizures</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypoxia-ischæmia</strong></td>
<td></td>
</tr>
<tr>
<td>− prenatal (toxaemia, abruptio placentae, cord compression)</td>
<td>++++++</td>
</tr>
<tr>
<td>− perinatal (iatrogenic, maternal haemorrhage)</td>
<td></td>
</tr>
<tr>
<td>− postnatal (cardio-respiratory causes such as hypoxic respiratory failure, congenital heart disease, pulmonary hypertension)</td>
<td></td>
</tr>
<tr>
<td><strong>Haemorrhage and intracerebral infarction</strong></td>
<td>+++</td>
</tr>
<tr>
<td>− intraventricular haemorrhage and haemorrhagic parenchymal infarction (mainly preterm neonates)</td>
<td></td>
</tr>
<tr>
<td>− intracerebral haemorrhage (spontaneous, traumatic)</td>
<td></td>
</tr>
<tr>
<td>− subarachnoid</td>
<td></td>
</tr>
<tr>
<td>− subdural haematoma</td>
<td></td>
</tr>
<tr>
<td>− perinatal arterial ischaemic stroke (PAIS)</td>
<td></td>
</tr>
<tr>
<td>− cerebral venous sinus thrombosis (CVST)</td>
<td></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>+++</td>
</tr>
<tr>
<td>− encephalitis, meningitis, brain abscess</td>
<td></td>
</tr>
<tr>
<td>− intrauterine (rubella, toxoplasmosis, syphilis, viral – such as cytomegalovirus, herpes simplex virus, human immunodeficiency virus, coxsackie virus B)</td>
<td></td>
</tr>
<tr>
<td>− postnatal (beta-haemolytic streptococci, Escherichia coli, herpes simplex virus, mycoplasma)</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>+++</td>
</tr>
<tr>
<td>− hypoglycaemia (glucose levels &lt;2.6mmol/l in a symptomatic full-term baby)</td>
<td></td>
</tr>
<tr>
<td>− hypocalcaemia &lt;1.75mmol/l (early, in first 2–3 days, mainly in preterm neonates with prenatal or perinatal insults; late, at 5–14 days, is mainly nutritional; maternal hyperparathyroidism; DiGeorge syndrome)</td>
<td></td>
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<tr>
<td>− hypomagnesaemia &lt;0.6mmol/L (may accompany or occur independently of hypocalcaemia)</td>
<td></td>
</tr>
<tr>
<td>− hyponatraemia (mainly associated with prenatal or perinatal insults; inappropriate secretion of antidiuretic hormone)</td>
<td></td>
</tr>
<tr>
<td>− hypernatraemia (mainly nutritional or iatrogenic)</td>
<td></td>
</tr>
<tr>
<td>− neonates of diabetic and toxaemic mothers</td>
<td></td>
</tr>
<tr>
<td>− pancreatic disease</td>
<td></td>
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</tbody>
</table>

**Drug withdrawal and toxic** | +++ |
– Withdrawal from: sedative-hypnotics, alcohol, heroin and methadone, narcotic-analgesics, barbiturates.

<table>
<thead>
<tr>
<th>Inborn Errors of Metabolism that may cause neonatal seizures</th>
</tr>
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<tbody>
<tr>
<td>– aminoacidopathies (especially non-ketotic hyperglycinaemia)</td>
</tr>
<tr>
<td>– organic acidopathies (especially Maple syrup urine disease)</td>
</tr>
<tr>
<td>– hyperammonaemic states (including urea cycle defects and some aminoacidopathies)</td>
</tr>
<tr>
<td>– sulphite oxidase deficiency and molybdenum cofactor deficiency</td>
</tr>
<tr>
<td>– lactic acidosis and mitochondrial disease</td>
</tr>
<tr>
<td>– congenital disorders of glycosylation</td>
</tr>
<tr>
<td>– creatine deficiency*</td>
</tr>
<tr>
<td>– pyridine/pyridoxal phosphate dependent seizures*</td>
</tr>
<tr>
<td>– folinic acid responsive seizures*</td>
</tr>
<tr>
<td>– biotinidase deficiency*</td>
</tr>
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<td>– GLUT-1 glucose transporter deficiency*</td>
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*all potentially treatable metabolic causes of neonatal onset epilepsies

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<thead>
<tr>
<th>Neurocutaneous syndromes</th>
</tr>
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<tbody>
<tr>
<td>– tuberous sclerosis, incontinentia pigmenti, Sturge-Weber syndrome</td>
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<table>
<thead>
<tr>
<th>Early onset epileptic encephalopathies/Neurogenetic encephalopathies*</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Early infantile epileptic encephalopathy (Ohtahara syndrome), incl CDKL5, KCNQ2, SCN2A.</td>
</tr>
<tr>
<td>– Early myoclonic encephalopathy (often associated with metabolic conditions, but also genetic cause’s incl ErbB4).</td>
</tr>
</tbody>
</table>

*the ILAE currently classifies the early onset epileptic encephalopathies by clinical and neurophysiological presentation; while there are a growing number of neurogenetic causes, there is overlap between these epilepsies and other causes of neonatal seizures – particularly structural and inborn errors of metabolism.

<table>
<thead>
<tr>
<th>Malformations of cerebral development</th>
</tr>
</thead>
<tbody>
<tr>
<td>– all disorders of neuronal induction, segmentation, migration, myelination and synaptogenesis such as polymicrogyria, neuronal heterotopias, liss-, holopros-, and hydranencephaly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Idiopathic benign neonatal seizures (familial and non-familial)</th>
</tr>
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4. MANIFESTATION OF NEONATAL SEIZURES

The clinical expression of seizure activity in the newborn is less well organised than in older infants, particularly in the preterm infant, when seizure manifestations are fragmentary and frequently indistinguishable from normal clinical activity.

A consensus statement on neonatal EEG terminology by the American Clinical Neurophysiology Society defined three types of neonatal seizures:\[12\]:

1) **Clinical-only seizures** in which there is a sudden paroxysm of abnormal clinical change that does not correlate with a simultaneous EEG seizure.

2) **Electro-clinical seizures** in which there is a clinical seizure coupled with an associated EEG seizure.

3) **EEG-only seizures** in which there is an EEG seizure that is not associated with any outwardly visible clinical signs. EEG-only seizures are also referred to as *subclinical, nonconvulsive, or occult seizures*.

Neonatal EEG seizures are described as having (1) sudden EEG change; (2) repetitive waveforms that evolve in morphology, frequency, and/or location; (3) amplitude of at least 2 µV; and (4) a duration of at least 10 seconds.

The International League Against Epilepsy (ILAE) updated its recommendations on seizure classification in 2017\[13\]; in this classification neonatal seizures are classified by the same scheme used for seizures in older patients. Two major limitations in this approach are that a) there is no clear position for subtle seizures, which are common in the neonate and the term is frequently used throughout the literature and b) there is an equal emphasis on focal and generalised seizures, although the vast majority of neonatal seizures are focal or multi-focal in nature.

A consensus statement from the ILAE regarding neonatal seizures has been presented, but to date not published. This statement assumes all neonatal seizures to be focal and is subdivided into those with clinical signs and those without. Seizures with clinical signs are further divided into:

- **Motor**
  - Automatisms
  - Clonic
  - Epileptic spasms
  - Myoclonic
  - Sequential
  - Tonic

- **Non-Motor**
  - Autonomic
  - Behavioural Arrest

- **Unclassified**
As this is not yet published, this guideline retains the simple classification described by Volpe, with four clinically evident seizure types as well as a critical fifth type of EEG-only seizures:

1. Subtle seizures
2. Clonic - focal or multifocal.
3. Tonic seizures.
4. Myoclonic - generalized or focal.

Seizures need to be differentiated from jitteriness and conditions like benign neonatal sleep myoclonus.

It should be noted that despite great efforts to carefully describe the appearances of neonatal seizures, inter-rater agreement in neonatal seizure identification by clinical observation is suboptimal, 

emphasising the need for continuous video-EEG monitoring to accurately identify seizure activity in the newborn.

### 4.1 Subtle Seizures

(10-35% depending on maturity); more common in term babies – particularly in infants following severe global insult (e.g. HIE).

- Ocular movements (rhythmic or irregular eye movements, sustained eye deviation or fixation of gaze, eye lid blinking or fluttering, eye opening, eye rolling up, nystagmus).
- Oral-buccal-lingual movements (chewing, sucking, smacking, tongue protrusions).
- Progression movements (rowing, peddling, bicycling, thrashing), symmetric or asymmetric.
- Complex purposeless movements (repetitive facial movements, sudden arousal, episodic limb hyperactivity and crying).
- Autonomic (apnoea, tachycardia, unstable blood pressure).

### 4.2 Multifocal & Focal Clonic Seizures

(50%); more common in term infants.

- Rhythmic movements of muscle groups.
- Rapid twitch followed by a slow relaxation.
- May involve face, tongue, limbs, and diaphragm.
- Focal clonic seizures can be caused by focal CNS pathology – e.g. cerebral haemorrhage/infarct.
- Consciousness usually preserved.

### 4.3 Tonic Seizures

(20%); more common in preterm infants.

- Sustained contraction (flexion or extension) of facial, limb, axial or other muscle groups; they may be focal, multifocal or generalized, symmetrical or asymmetrical.
- Decerebrate posturing.
- Dystonic posturing.
- Focal tonic head or eye turning.
4.4 Myoclonic Seizures

- Rapid isolated jerks of single extremity, multifocal, or generalized (may affect a finger, limb or whole body).
- Myoclonic seizures seen in drug withdrawal (particularly opiates).
- *Benign neonatal sleep myoclonus* is normal and seen in healthy pre-term and term infants occurring during active sleep; it ceases on waking the baby. It usually resolves within 2 months, although can go on for longer.

4.5 Non-Seizure Symptoms that Mimic Seizures

- Jitteriness
  - Rapid symmetric to-and-fro motion.
  - Fast rhythmic movements.
  - Occur when awake and asleep.
  - Can occur in normal and abnormal infants.
  - Jitteriness is not associated with ocular deviation. It is stimulus sensitive (e.g. easily stopped with passive movement of the limb). The movement resembles a tremor, and no autonomic changes are associated with it.
  - Seizures are often associated with ocular deviation and are not stimulus sensitive. Autonomic changes frequently accompany seizures. The movements are clonic, unlike the tremor-like movements of jitteriness.

- Apnoea
  - May be a manifestation of subtle seizure, more likely in a term infant and associated with eye deviation or staring.
5. **DIAGNOSIS**

Neonatal seizures are a common neonatal emergency. Confirmation of seizures should initiate urgent and appropriate clinical and laboratory evaluation for aetiological cause. Family history, prenatal and birth history is important. A full clinical examination should be carried out along with urgent comprehensive biochemical tests for correctable metabolic disturbances.

*It is important to involve Paediatric Neurologists early in the investigation and management of neonatal seizures, particularly as they can guide specialist investigations.*

5.1 **History & Examination**

- Antenatal history: routine anomaly scans; illness during pregnancy; frequency and character of movements in utero (classically seizures in utero can mimic hiccoughs); maternal drug abuse; maternal diabetes; history of infections (including herpes genitals).
- Perinatal and birth history: prolonged rupture of membranes; eclampsia; birth trauma; foetal distress (CTG, scalp pH, cord gases including lactate and need for resuscitation).
- Postnatal history: document the nature and duration of seizures, attach aEEG if available.
- Examination: assess neurological state. Note any cutaneous lesions, bruits etc. Measure head circumference.

5.2 **Investigations**

5.2.1 **First Line**

<table>
<thead>
<tr>
<th>Initial laboratory evaluation: <em>metabolic</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glucose</td>
</tr>
<tr>
<td>2. Ionised calcium, sodium, phosphate, magnesium</td>
</tr>
<tr>
<td>3. Liver function &amp; creatinine</td>
</tr>
<tr>
<td>4. Blood gas (pH, bicarbonate, lactate)</td>
</tr>
<tr>
<td>5. Serum bilirubin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial laboratory evaluation: <em>infections</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FBC</td>
</tr>
<tr>
<td>2. CRP</td>
</tr>
<tr>
<td>3. Blood and urine culture (including PCR for herpes simplex)</td>
</tr>
<tr>
<td>4. CSF analysis – microscopy &amp; culture, PCR for herpes simplex, neurotropic viruses including enterovirus</td>
</tr>
</tbody>
</table>

Consider saving CSF sample for further metabolic testing e.g. Glycine: *Discuss with local laboratory*
Initial evaluation: *neurophysiology and neuroimaging*

1. Amplitude integrated electroencephalography (aEEG, sometimes known as cerebral function monitor (CFM)) please see CFM guideline on Intranet (East of England reference: EOE-005-2017)
2. Continuous (video)-electroencephalography (EEG)*
3. Cranial ultrasound

* The longer the duration of continuous EEG monitoring, the more useful the investigation, however this has to be balanced against neurophysiology resources available locally.

The aEEG and EEG are complimentary investigations as a full EEG can provide much more information than aEEG alone.

5.2.2 Second line

Depending on the first line investigation results, further investigations should be considered:

### Laboratory investigations: *metabolic*

1. Thyroid function test
2. Urate (*molybdenum cofactor deficiency*)
3. Plasma amino acids (*amino acid disorders*)
4. Urine organic and amino acids (*organic/amino acid disorders*)
5. Acylcarnitine (*Fatty acid oxidation defects*)
6. Very long chain fatty acids (*peroxisomal defects*)
7. Ammonia (*urea cycle defects*)*
8. Biotinidase (*biotinidase deficiency*)**

### Maternal drug abuse: toxicology screen

1. Maternal urine sample
2. Neonatal urine sample

### Further imaging/investigation

1. MRI
2. Formal Ophthalmological examination
3. Woods Light examination
4. Consider genetic testing/congenital infection (TORCH) screen if indicated

* Usually presents with neonatal encephalopathy

** Rarely presents in the neonatal period

5.2.3 Third line
Suggested third line investigations for refractory seizures: consider metabolic screen for possible inborn errors of metabolism; thrombophilia screen for suspected neonatal stroke.

**Laboratory investigations: metabolic**

1. CSF Glycine (*glycine encephalopathy*)
2. CSF sulphocysteine (*Mb Cofactor/Sulphite oxidase deficiencies*)
3. CSF pipecolate (*Pyridoxine dependent seizures*)
4. Urine AASA (*Pyridoxine dependent seizures*)
5. CSF pyridoxal phosphate (*Pyridoxal phosphate dependent seizures*)

**Laboratory investigations: thrombophilia screen***

1. Protein C
2. Protein S
3. Antithrombin III
4. Anticardiolipin antibodies
5. Factor V Leiden FV G1691A mutation
6. G2021A Prothrombin variant
7. Polymorphism in methylenetetrahydrofolate reductase (MTHFR) gene

*The value of a thrombophilia screen in the neonate is controversial and should be discussed with a Paediatric Neurologist and Paediatric Haematologist regarding the indication and timing of these investigations.*
6. MANAGEMENT

6.1 General Management

- Airway
- Breathing
- Circulation
- Treat any underlying cause as a matter of urgency: correction of hypoglycaemia, electrolyte disturbances and treat infection.

Cardiorespiratory symptoms may result from underlying disease, from the seizures or from anticonvulsant medication.

- Hypoglycaemia – 2.5ml/kg 10% Dextrose IV bolus followed by maintenance infusion of 10% Dextrose.
- Hypocalcaemia - Calcium gluconate 10% 2ml/kg (0.46mmol/kg) over 5-10 minutes IV with ECG monitoring.
- Hypomagnesaemia – Magnesium sulphate 50% 0.2 ml/kg (0.4mmol/kg) by deep intramuscular injection or Magnesium sulphate 10% (0.4mmol/kg) by IV infusion over 10 minutes.

6.2 Anticonvulsant drug therapy – overview

6.2.1 Evidence

Little evidence supports the use of any of the anticonvulsant drugs currently prescribed in the neonatal period and there is a lack of consensus regarding the optimal treatment protocol. Early and accurate seizure detection is important for guiding anticonvulsant drug therapy: neurophysiological assessment (aEEG or EEG) can be extremely useful for this purpose, particularly given the phenomenon of electro-clinical dissociation.

Data regarding the efficacy and safety of anticonvulsant medications come from retrospective studies using highly variable methodologies. Phenobarbital still remains the most widely used first line agent; a randomised crossover trial of 59 infants with EEG-confirmed seizures, showed a reduction of severity of seizures by 43%, which increased to 57% when combined with phenytoin. High dose phenobarbital has been shown to induce apoptosis in animal models; however, as infants treated with phenobarbital are already at high risk of developmental delay and behavioural impairment, it has been difficult to prove whether phenobarbital has a harmful or beneficial effect in the long term. There is currently no evidence that prophylactic phenobarbital has a neuroprotective effect.
The use of phenytoin has declined dramatically in recent years, mainly due to concerns of cardiac side effects\textsuperscript{18}. Nevertheless, it has a similar efficacy to phenobarbital\textsuperscript{19}. It is metabolised by the liver and as such plasma concentrations may be increased with therapeutic hypothermia, although no pharmacokinetic studies have been performed. Conversely, the use of levetiracetam has increased tenfold in the past decade, probably resulting from its efficacy in children and adults and wide safety margin. However, there is limited data from neonates, with only retrospective studies showing a decrease in seizures of around 30\%\textsuperscript{20}. Midazolam is still widely used, however again there is a paucity of neonatal data, mainly from retrospective studies showing a reduction of around 20\%\textsuperscript{21}. Lidocaine is widely used in Europe, but less so in the USA; the main concern is the risk of cardiac arrhythmias (the reported incidence varies from 0.4-4.8\%) and should not be used in the presence of cardiac dysfunction or with phenytoin\textsuperscript{22,23}. Efficacy data is poor, with multiple small single centre (mostly retrospective) studies reporting efficacy ranging from 20\% to 91\%\textsuperscript{24}. Finally, Topiramate, although widely used in adults and children has not been used as much in neonates, mainly because until recently there was no parenteral formulation\textsuperscript{25}. Further studies are required, but animal studies have demonstrated a neuroprotective role following hypoxia-ischaemia, stroke and refractory seizures, making it a potentially promising drug\textsuperscript{26,27}. For a more detailed review of neonatal pharmacotherapy see reviews by Donovan et al. and El-Dib et al.\textsuperscript{28,29}.

### 6.2.2 Initiation

Uncertainty exists over when to commence anticonvulsant drugs. Anticonvulsant drugs should be considered to treat seizures, once any underlying metabolic disturbances have been corrected, if they are:

- Associated with cardiorespiratory compromise.
- Prolonged: greater than 3 minutes.
- Frequent: greater than 3 per hour.

Because of the high frequency of EEG-only seizures continuous aEEG or EEG monitoring should be commenced if seizures are suspected and electrical seizures treated in the same manner as clinical only or electro-clinical seizures. Ideally neurophysiological monitoring should be commenced before anticonvulsants are administered, unless the infant is cardiorespiratory compromised by the seizure, as many anti-convulsants will alter the background activity of the EEG making subsequent neurophysiological assessment difficult.
Beware of potential short-term side effects of anticonvulsants – e.g. respiratory/myocardial/neurological depression as well as potential long-term effects, such as reduced cognition and memory in children following prolonged administration.

6.2.3 Administration
Administer anticonvulsant drugs:
- Intravenously to achieve rapid onset of action and more predictable blood levels.
- To achieve serum levels in the high therapeutic range.
- If there is no IV access and glucose and electrolyte abnormalities have been excluded, consideration should be given to intranasal or buccal midazolam.

6.2.4 Maintenance and duration of treatment
The duration of anticonvulsant drug treatment should be as short as possible; however, this will depend on the diagnosis and the likelihood of seizure recurrence. Maintenance therapy may not be required if loading doses of anticonvulsant drugs control clinical seizures. If maintenance therapy is considered serum levels should be monitored (in drugs where an assay is available).

6.2.5 Cessation of treatment
There is a low risk of seizure recurrence after early withdrawal of anticonvulsant medication in the neonatal period (e.g. following HIE). Consider ceasing anticonvulsant drugs:
- Once seizures have ceased and the neurological examination is normal.
- If the neurological examination remains abnormal but the EEG is normal.

For babies discharged home on anticonvulsants, withdrawal is undertaken at the earliest opportunity when clinical neurological recovery occurs (usually within 6-8 weeks). If abnormal neurology persists, anticonvulsants may be continued for up to six months, but an attempt should be made to withdraw phenobarbital by that time, and, if seizures recur, a more appropriate anticonvulsant should be introduced.
6.3 Anticonvulsant drug therapy – specific drugs

6.3.1 Intranasal/buccal Midazolam
- Consider if no IV access and glucose and electrolyte abnormalities have been excluded.
- **Dose:** 300 microgram/kg single does.
- **Notes:** can be repeated once; wait 10 minutes before repeating. Ensure cardiorespiratory status stable.

6.3.2 Phenobarbital (phenobarbitone)
- Drug of first choice.
- **Loading dose:** 20 mg/kg IV as a loading dose slowly over 20 minutes. Repeat a second loading dose of 10-20 mg/kg IV if baby continues to have seizures (max. total dose 40mg/kg).
- **Maintenance dose:** 2.5-5mg/kg IV/oral once daily beginning 12-24 hours after loading dose. Where a high loading dose has been used, no daily maintenance dose should be started for at least 3-4 days (especially if there has been intrapartum asphyxia).
- **Therapeutic range:** Measure trough levels 48 hours after loading dose. Aim for therapeutic levels of 20–40 micrograms/ml (90-160 micromols/l). Phenobarbital has a long half-life (2-4 days) in neonates and levels can take a long time to stabilise or come down.
- **Note:** shown to be effective in less than 50%; clinical seizures may not be apparent after phenobarbital, however, electrical seizures could still persist. May cause apnoea/respiratory depression at high doses (40mg/kg) and high serum concentrations (>60 micrograms/ml).
  If administered enterally then an alcohol free solution must be used.

If no response to phenobarbital – options are:

6.3.2 Levetiracetam
- **Loading dose:** 20mg/kg (IV infusion over 15 minutes); can be repeated if seizures persist to give a total dose of 40mg/kg.
- **Maintenance:** 10-15mg/kg/dose twice a day IV/oral.
- **Note:** Halve the maintenance dose in infants with severe renal impairment (creatinine >150 micromol/L).

6.3.3 Phenytoin
- **Loading dose**: 20mg/kg (slow IV infusion over 30 minutes, i.e. <1 mg/kg/min).
- **Maintenance**: 2.5-5mg/kg/dose twice a day IV/oral after loading dose; after 1 week of age up to 7.5mg/kg/dose twice a day.
- **Therapeutic range**: measure trough levels 48 hours after IV loading dose. Aim for therapeutic levels of 5-15 mg/L (20-60 micromol/L)

It is a protein-bound drug, so levels may fluctuate in neonates. In addition the changes in volume of distribution in neonates can make it hard to achieve stable levels with maintenance doses.

- **Notes**: ensure integrity of IV due to potential for tissue inflammation, necrosis with extravasation. Administer slowly IV (maximum rate 1mg/kg/min) to avoid cardiac arrhythmias. Monitor cardiac rate, rhythm and blood pressure for hypotension. Dilution of IV phenytoin may be required to accurately administer doses to neonates. Dilution should be with sodium chloride 0.9% not exceeding a concentration of 10mg/ml. Administration of diluted solution should be via a 0.22-0.5micron filter.

### 6.3.3 Midazolam

- **Dose**: 150-200 micrograms/kg as a slow IV injection over 5 minutes followed by a continuous infusion at 60 micrograms/kg/hour increasing by 60 micrograms/kg/hour every 15 mins until seizures are controlled (max 300 micrograms/kg/hour).
- **Note**: May be effective in babies who continue to seize after phenobarbital and/or phenytoin.

May cause myoclonic jerking and dystonic posturing in preterm infants - hence concerns regarding its use in preterm infants. Also be aware that accumulation due to prolonged elimination in neonates can occur.
Also consider following discussion with Paediatric Neurologists:

6.3.6 Lidocaine (lignocaine)

- Loading dose: 2mg/kg IV over 10 minutes, then commence an infusion
- Infusion: 6mg/kg/hour for 6 hours, then 4 mg/kg/hour for 12 hours, then 2mg/kg/hour for 12 hours. Pre-term neonates may require lower doses.
- Notes: Avoid giving to infants also treated with Phenytoin due to possible cardiac effects. Ensure continuous monitoring of heart rate, rhythm and blood pressure.

6.3.8 Pyridoxine

- If recurrent seizures with no obvious cause, consider Pyridoxine dependency. Give a trial of Pyridoxine 50 -100 mg IV, (total dose) with EEG monitoring. Seizures can stop within minutes in true dependency, however interpretation of effect is not always straightforward: it may take between 72 hours – 1 week of treatment before a definitive conclusion can be made. Sometimes it may be responsive only to pyridoxal phosphate and not pyridoxine.
- The first dose of pyridoxine in a neonate can cause hypotonia or apnoea requiring support.

6.3.9 Pyridoxal-5-phosphate

- This is only administered as an oral medication as no IV preparation is available.
- Usual dose is 10mg/kg/dose three times a day (max five times a day). The 50mg tablets need to be crushed finely and dispersed in at least 20ml of water, so that the required dose can be administered via a feeding tube.
- Sudden respiratory arrest and profound hypotension may occur. Initial patient monitoring includes baseline observations and continuous cardiac and saturation monitoring. Blood pressure, pulse, respirations and oxygen saturation should be monitored every 15 minutes for 2-3 hours following administration of the first dose.

6.3.10 Other Inborn Errors of Metabolism
There are specific treatments for certain inborn errors of metabolism, which should be discussed with the Paediatric Neurologists and regional metabolic centre\textsuperscript{40}. For example Folinic acid responsive seizures (which may show a transient response to pyridoxine) and Biotinidase deficiency, responsive to Biotin. It is important that the relevant investigations (e.g. serum folate, CSF neurotransmitters and plasma biotinidase) are sent off prior to administration of these vitamins.

7. Prognosis

Prognosis is cause dependent. Despite high mortality (approximately 15\%) and morbidity (approximately 50\%) one half of the neonates with seizures achieve a normal or near normal outcome. About one third develop epilepsy.
REFERENCES

13. www.ilae.org/guidelines


<table>
<thead>
<tr>
<th>No.</th>
<th>RECOMMENDATIONS</th>
<th>Strength</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Clinically apparent seizures in the neonate should be treated if they last more than 3 minutes or are brief serial seizures. In specialized care facilities where electroencephalography is available, all electrical seizures, even in the absence of clinically apparent seizures, should also be treated.</td>
<td>Strong</td>
<td>Not graded</td>
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<td>Strong, context-specific</td>
<td>Not graded</td>
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<tr>
<td>2.</td>
<td>In all neonates with seizures, hypoglycaemia should be ruled out and treated if present before antiepileptic drug treatment is considered. If facilities for measuring glucose are not available, consider empirical treatment with glucose. If there are clinical signs suggestive of associated sepsis or meningitis, central nervous system infection should be rule out by doing a lumbar puncture, and treated if present with appropriate antibiotics. If facilities for lumbar puncture are not available, consider empirical treatment with antibiotics for neonates with clinical signs of sepsis or meningitis. In all neonates with seizures, serum calcium should be measured (if facilities are available) and treated if hypocalcaemia is present. In the absence of hypoglycaemia, meningitis, hypocalcaemia or another obvious underlying etiology such as hypoxic-ischaemic encephalopathy, intracranial haemorrhage or infarction, pyridoxine treatment may be considered before antiepileptic drug treatment in a specialized centre where this treatment is available.</td>
<td>Strong</td>
<td>Not graded</td>
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<td></td>
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<td>Weak, context-specific</td>
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<td>Weak, context-specific</td>
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<tr>
<td>3.</td>
<td>Phenytoin should be used as the first-line agent for treatment of neonatal seizures; phenobarbital should be made readily available in all settings.</td>
<td>Strong</td>
<td>Very low</td>
</tr>
<tr>
<td>4.</td>
<td>In neonates who continue to have seizures despite administering the maximal tolerated dose of phenobarbital, either a benzodiazepine, phenytoin or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring facilities)</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>5.</td>
<td>In neonates with normal neurological examination and/or normal electroencephalography, consider stopping antiepileptic drugs if neonate has been seizure-free for &gt;72 hours; the drug(s) should be reinstituted in case of recurrence of seizures.</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>6.</td>
<td>In neonates in whom seizure control is achieved with a single antiepileptic drug, the drug can be discontinued abruptly without any tapering of the dose. In neonates requiring more than one antiepileptic drug for seizure control, the drugs may be stopped one by one, with phenobarbital being the last drug to be withdrawn.</td>
<td>Weak</td>
<td>Not graded</td>
</tr>
<tr>
<td>7.</td>
<td>In the absence of clinical seizures, neonates with hypoxic-ischaemic encephalopathy need not to be given prophylactic treatment with phenobarbital.</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>8.</td>
<td>Where available, all clinical seizures in the neonatal period should be confirmed by electroencephalography. Electroencephalography should not be performed for the sole purpose of determining the etiology in neonates with clinical seizures.</td>
<td>Strong, context-specific</td>
<td>Not graded</td>
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<td>9.</td>
<td>Radiological investigations (ultrasound, computed tomography and magnetic resonance imaging) of the cranium/head should not be performed to determine the presence or absence of clinical seizures or to evaluate the efficacy of treatment with antiepileptic drugs in neonates. Radiological investigations may be done as a part of the comprehensive evaluation of the etiology of neonatal seizures or to determine prognosis in neonates with seizures.</td>
<td>Strong</td>
<td>Not graded</td>
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<td>Weak, context-specific</td>
<td>Not graded</td>
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</table>
Suspected Seizures

Check Glucose and treat hypoglycaemia

2.5ml/kg 10% Dextrose IV bolus followed by maintenance infusion of 10% Dextrose

aEEG/EEG monitoring

If no IV access consider buccal/intranasal Midazolam

First Line Treatment

Maximal Loading Dose Phenobarbital 30mg/kg

Phenobarbital

Continuing Seizures

Assess clinical and aEEG/EEG response

Phenobarbital

Continuing Seizures

Assess clinical and aEEG/EEG response

Second Line Treatment

One of these three options

Consider discussion with Paediatric Neurologist and escalation of care

Midazolam

Levetiracetam

Phenytoin

Continuing Seizures

Assess clinical and aEEG/EEG response

Complete loading dose of any 2nd line drugs

Continuing Seizures

Assess clinical and aEEG/EEG response

Third Line Treatment

Unknown cause

Use other options of second line treatments

Known cause

Or consider Lidocaine if Phenytoin not used

Pyridoxal Phosphate/Pyridoxine
Also consider Folic Acid/Biotin under direction of Paediatric Neurologists