



East of England Neonatal ODN

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East of England Neonatal Neuroprotection Guideline

Diagnosis & Management of Neonatal Seizures in the Term Infant

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Registration No: NEO-ODN-2026-22

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1. INTRODUCTION

- The International League Against Epilepsy (ILAE) provided a new classification in 2021¹ and recommendations for management of seizures in the neonatal period in 2023².
- It provided evidence and consensus-based recommendations to neonatal seizure management including first line and second line anti-seizure management, duration of treatment and administration of pyridoxine.
- The guideline focuses on these changes and definitions.

2. BACKGROUND

- Seizures are the most common neurological emergencies in the neonatal period with an incidence of 1-5 per 1000 live births and even a high incidence in preterm infants of 10-130 per 1000 live births ².
- Majority of the neonatal seizures have an underlying aetiology¹.
- Neonatal seizure may be the first clinical sign of a serious neurologic disorder hence rapid recognition and evaluation are required to identify and treat the underlying aetiology, prevent further brain injury, and decrease seizure activity.^{1 3 4}
- Seizures in the developing brain have been shown to be an independent risk factor for adverse neurodevelopmental outcome ^{5 6}.
- Diagnosis can be difficult due to the seizures' subtlety. Some normal infant movements may be misdiagnosed as seizures, while some seizures are overlooked as normal movements. As a result, using only clinical observations to diagnose neonatal seizures is not appropriate.
- 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, do not reduce the electrical discharge⁷ (electro-clinical dissociation or uncoupling).
- There is wide variation in clinical practice in both diagnosis and treatment of 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.



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3. DEFINITIONS

NEONATAL SEIZURE: an electrographic event with a pattern characterised by sudden, repetitive, evolving stereotyped waveforms with a beginning and end. The duration is not defined but it must be sufficient to demonstrate evolution in frequency, voltage and morphology of the discharges and needs to be long enough to allow recognition of onset, evolution and resolution of an abnormal discharge ¹. Practically >10-20 seconds duration is considered sufficient duration.

ACUTE PROVOKED SEIZURE: Seizure provoked by an acute illness or neurological insult with an underlying aetiology (Previously called acute symptomatic seizures).

EPILEPSY: At least 2 unprovoked seizures occurring >24 hours apart or one unprovoked seizure and a probability of further seizures similar to the general recurrence risk after 2 unprovoked seizures or diagnosis of epilepsy syndrome ¹.

SEIZURE BURDEN: Is defined as ictal (or seizure) electrographic activity in a given period of EEG recording and expressed as summed electrographic seizure seconds in a given period. It is the seizure burden that is associated with poor outcome ¹.

SEIZURE FREQUENCY: Is defined as number of seizures in a given time period.

STATUS EPILEPTICUS: Currently there is no standard definition for neonatal status epilepticus. American Clinical Neurophysiology Society (ACNS) defines status epilepticus as summed duration of electrographic seizures comprises $\geq 50\%$ of any 1 hr epoch. This is currently being looked at by ILAE ⁸.

4. AETIOLOGY

- Majority of the neonatal seizures acute provoked seizures ¹.
- In term infants, the most common causes of seizures are hypoxic-ischaemic encephalopathy (HIE), ischaemic stroke and intracranial haemorrhage; in extremely

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preterm infants, the most common cause is intracranial haemorrhage².

- Cause of the seizures determines the prognosis, as well as the treatment strategy.

Common causes are listed in table 1⁹ below.

Table 1 Contribution of causes of neonatal seizures	Frequency(%)
Hypoxia-ischaemia encephalopathy	30-53
Intracranial haemorrhage	7-17
Cerebral infarction	6-17
Cerebral malformations	3-17
Meningoencephalitis	2-14
Metabolic	
– hypoglycaemia	0.1-5
– hypocalcaemia , hypomagnesaemia (may accompany or occur independently of hypocalcaemia)	4-22
– hypo/hyponatraemia	3-4
– inborn errors of metabolism (pyridoxine dependency, folinic acid responsive seizures, glucose transporter defect, non-ketotic hyperglycinaemia, propionic aciduria.	
- Kernicterus	1
Maternal drug withdrawal	4
Idiopathic	4
Self-limited neonatal (familial) epilepsy (SeLNE/SeLFNIE) (previously called benign)	2
Developmental and Epileptic encephalopathy (DEEs)	1

5. CLASSIFICATION OF NEONATAL SEIZURES¹

- The clinical manifestation of seizures in neonates is often less organised and more subtle than in older infants, particularly in preterm infants, where signs may be fragmentary and difficult to distinguish from normal behaviours or non-epileptic phenomena
- Due to this variability, diagnosis based on clinical observation alone is unreliable. Inter-rater agreement on seizure recognition based on observation was shown to be poor

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- ¹⁰, and many clinical events once assumed to be seizures are now known not to correlate with EEG activity. Many neonates will have mostly or exclusively electrographic seizures which will only become apparent on EEG or aEEG.
- In neonates continuous video EEG recording is the gold standard for diagnosis¹¹, however it is recognised that many neonatal units have limited or no access to EEG. Amplitude integrated EEG (aEEG), available in all neonatal units as a bedside tool, can be used instead although its limitations should be recognised.
 - The previously used terms such as “subtle seizures” are no longer part of the ILAE classification due to their inconsistent electrographic correlation. Movements such as ocular deviation, oral-buccal-lingual automatisms, and complex behaviours should only be considered seizures if accompanied by EEG confirmation.
 - It is also now recognized that the vast majority of neonatal seizures are focal in origin, even in diffuse pathologies like HIE. The concept of “generalised seizures” has limited application in the neonatal period.
 - In summary, accurate identification of neonatal seizures requires continuous video-EEG or amplitude-integrated EEG (aEEG) monitoring wherever feasible. Clinical observation remains important but must always be interpreted alongside EEG to confirm the presence and type of seizure activity.

5.1. Current Classification of Seizures based on the ILAE Task Force on Neonatal Seizures¹: (Fig 1)

- **Electrographic-only seizures:** Seizure seen on EEG without any clinical signs (previously called subclinical seizures).
- **Electro-clinical seizures:** Accompanied by observable clinical features with EEG correlation.

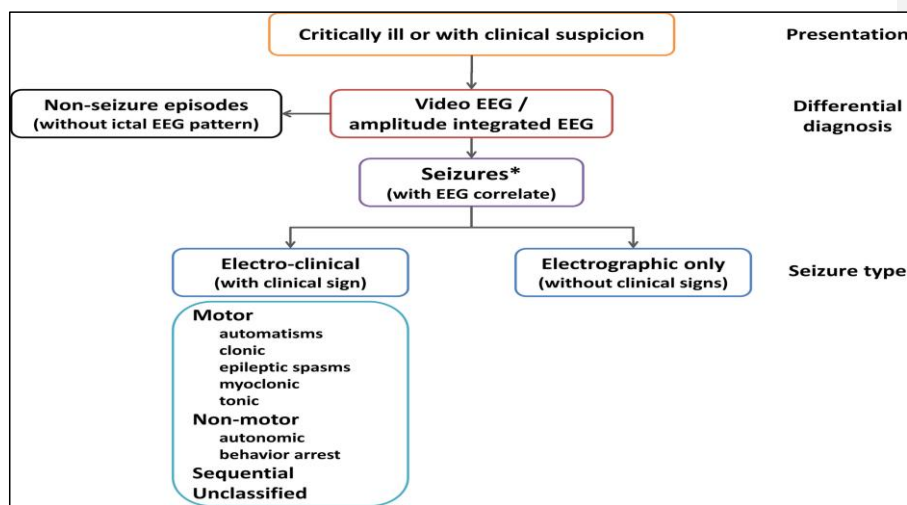
Electroclinical seizures are further categorized based on predominant semiology into:

- **Motor** (e.g., clonic, tonic, myoclonic, automatisms, epileptic spasms)

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- **Non-motor** (e.g., autonomic, behaviour arrest)
- **Sequential** (where the seizure evolves through more than one type)
- **Unclassified**

Figure 1: Seizure classification



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Table 2: Description of Electroclinical seizures¹

Type	Description ^{6,7}	Special considerations	Clinical context of seizure type
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 preictal motor activity.	Typically oral in neonates. Behavior in term and preterm infants may mimic ictal automatisms, thus EEG / aEEG mandatory.	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.	Seizure type, which is more reliably diagnosed clinically.	Typical seizure type in neonatal stroke or cerebral hemorrhage. 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 without EMG channel. May occur in clusters.	Rare. May be seen in inborn errors of metabolism or early-infantile 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, requires EEG, ideally with EMG channels.	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. Generalized tonic posturing not of epileptic origin.	Typical seizure type early-infantile DEE and genetic neonatal epilepsies.
Autonomic	A distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, and thermoregulatory functions.	May involve respiration (apnea). EEG / aEEG mandatory.	Rare in isolation. Seen in intraventricular hemorrhage as well as temporal or occipital lobe lesions. Also described in early-infantile DEE.
Behavioral arrest	Arrest (pause) of activities, freezing, immobilization, as in behavior arrest seizure.	EEG / aEEG mandatory.	Rare as an isolated seizure type. More commonly seen as part of sequential seizure.
Sequential seizure	This term is used in the instruction manual for the ILAE 2017 operational classification of seizure types for events with a sequence of signs, symptoms, and EEG changes at different times. ⁶	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-limited neonatal epilepsy or KCNQ2 encephalopathy.

Electrographic-only Seizures

- Seizures with no visible clinical signs, identified solely on EEG/aEEG.
- Common in neonates with HIE (particularly in those with basal ganglia/thalamus injury), preterm infants, critically ill and neonates undergoing cardiac surgery.

5.2. Diagnosing seizures when EEG/aEEG is not available

- If only clinical evaluation is available, focal clonic seizures and focal tonic seizures observed by experienced personnel can be considered as 'probable seizures.
- Other clinical events would require EEG confirmation and can only be deemed as possible seizures.
- Generalised tonic extensor posturing events without clear asymmetry are not considered as seizures
- If stimulation provokes behaviours suspected to a clinical seizure and restraint of infant limb prompts arrest of these events, these are considered as non-epileptic events.



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5.3. Non-Seizure Events That Mimic Seizures

Benign neonatal sleep myoclonus

- Occurs during active (REM) sleep, with rapid, repetitive jerks affecting limbs or trunk.
- Resolves upon waking, with no EEG correlate.
- Self-limiting and not associated with neurodevelopmental impairment.

Jitteriness

- Rapid, low-amplitude tremor-like movements, typically stimulus-sensitive and symmetric.
- Not associated with autonomic signs or ocular deviation.
- Can be stopped by holding the affected limb; no EEG correlate.

Apnoea

- Apnoea with associated eye deviation or behavioural arrest may represent autonomic seizure.
- Requires EEG correlation for confirmation.

6. 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.

6.1. History & Examination

- Antenatal history: 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), family history of seizures.

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- Perinatal and birth history: prolonged rupture of membranes; eclampsia; birth trauma; foetal distress, 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.

6.2. Investigations

6.2.1. First Line (Table 3)

Initial laboratory evaluation: <i>metabolic</i>
1. Glucose 2. Ionised calcium, sodium, magnesium 3. Liver and renal function, bone profile 4. Blood gas (pH, bicarbonate, lactate) 5. Serum bilirubin
Initial laboratory evaluation: <i>infections</i>
1. FBC 2. CRP 3. Blood and urine culture (including PCR for herpes simplex) 4. CSF analysis – microscopy & culture, PCR for herpes simplex, viruses including enterovirus, CMV Consider saving CSF sample for further metabolic testing e.g. Glycine: <i>Discuss with local laboratory</i>

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Initial evaluation: neurophysiology and neuroimaging

1. Amplitude integrated electroencephalography (aEEG, sometimes known as cerebral function monitor (CFM) please see [CFM guideline](#) on the East of England ODN Website
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.*

A full EEG can provide much more information than aEEG alone.

6.2.2. Second line (Table 4)

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 acids (*organic 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. Consider congenital infection (TORCH) screen if indicated

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4. If no clear acquired cause (e.g. HIE, stroke, haemorrhage, infection, metabolic), or if seizures are refractory, tonic/sequential, associated with burst-suppression or unexplained encephalopathy, request rapid whole genome sequencing via the NHS Genomic Test Directory (R14 – acutely unwell children with a likely monogenic disorder; trio samples) after discussion with Clinical Genetics/Paediatric Neurology

* Usually presents with neonatal encephalopathy

** Rarely presents in the neonatal period

6.2.3. Third line (Table 5)

Suggested third line investigations for refractory seizures: consider metabolic screen for possible inborn errors of metabolism.

Laboratory investigations: *metabolic*

1. CSF Glycine (*glycine encephalopathy*)
2. CSF sulphocysteine (*Mb Cofactor/Sulphite oxidase deficiencies*)
3. CSF pipicolate (*Pyridoxine dependent seizures*)
4. Plasma and Urine AASA/P6C, Plasma pipicolonic acid (*Pyridoxine dependent seizures*)
5. CSF pyridoxal phosphate (*Pyridoxal phosphate dependent seizures*)

* 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.



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7. MANAGEMENT (Appendix 1)

7.1. 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 ml/kg 10% Glucose IV bolus followed by maintenance infusion of 10% Glucose
- 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.

7.2. Anti-seizure medication (ASM)– overview

7.2.1. Evidence ²

Little evidence supports the use of any of the ASM currently prescribed in the neonatal period. Early and accurate seizure detection is important for guiding anticonvulsant drug therapy. In addition, treatment with antiseizure medication may cause electro-clinical uncoupling in which clinical correlate ceases and electrographic seizures persist. Hence video EEG or at least aEEG is recommended for diagnosis and ongoing management and monitoring of seizures.

The **2023 ILAE Task Force²** provides international evidence and consensus-based guidance on first line and second-line therapies for neonatal seizures. While evidence

remains limited, the guidelines recommend standardised treatment pathways and support the treatment of electrographic-only seizures.

7.2.2. First line ASM:

In neonates with seizures requiring ASM, phenobarbital should be the first-line ASM irrespective of aetiology- moderate strength of evidence-based recommendation with a high level of consensus-based agreement

If channelopathy is likely the cause for seizures such as strong family history, then a sodium channel blocker should be considered as the first-line ASM.- (*high level of consensus-based agreement*).

Two RCT studies were included in the GRADE analysis.

The first study Painter et al¹² assessed the efficacy of phenobarbital and phenytoin for the treatment of seizures in term and preterm neonates with heterogeneous aetiologies. Study inclusion required EEG-confirmed seizure(s) and efficacy was evaluated by EEG monitoring. The primary outcome was complete seizure control within 24 hours. Seizures were controlled with phenobarbital in 13/30 (43%) and phenytoin in 13/29 (45%) neonates. There was no difference in efficacy between phenobarbital and phenytoin as first-line treatment (RR 0.97; 95%CI 0.54-1.72).

The second study Sharpe et al¹³ assessed the efficacy of phenobarbital and levetiracetam for the treatment of seizures in term neonates with heterogeneous aetiologies. Seizures were assessed by EEG monitoring for eligibility and efficacy. Initial dosing was 20 mg/kg for phenobarbital and 40 mg/kg for levetiracetam. Neonates who continued to have seizures (assessed every 15 minutes) received an additional 20 mg/kg of phenobarbital or an additional 20 mg/kg of levetiracetam. The primary outcome was seizure cessation on EEG within 15 minutes and sustained seizure free EEG for 24 hours after the infusion. Seizures were controlled with phenobarbital in 24/30 (80%) and levetiracetam in 15/53 (28%) neonates. Phenobarbital was more effective than levetiracetam as first-line treatment (RR 0.35; 95% CI 0.22–0.56); moderate certainty of evidence). No studies evaluated efficacy of ASM according to aetiology of acute symptomatic seizures.

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Most studies in the review (controlled and observational) did not report adverse events (n=9), but some (n=9) indicated that no adverse events were observed for phenobarbital, phenytoin and levetiracetam. One RCT¹² with phenobarbital and phenytoin reported that no adverse events were observed. Only one study¹³ with phenobarbital and levetiracetam used standardised adverse events tables and reported that there was a trend towards hypotension being more common with phenobarbital (n=17%) compared to levetiracetam (n=5%).

High dose phenobarbital has been shown to induce apoptosis in animal models¹⁴; 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 effect¹⁵. Post ILAE recommendations, recent metaanalyses do not change the phenobarbital first-line recommendation¹⁶.

7.2.3. Second Line ASM: The level of certainty of the evidence was very low regarding second-line ASM because of imprecision of estimates due to the very small number of patients included; consequently, expert opinion was sought via the Delphi process².

In neonates with seizures not responding to first-line antiseizure medication (ASM), phenytoin, levetiracetam, midazolam, or lidocaine may be used as a second-line ASM for most aetiologies (HIE, stroke, or haemorrhage). – (moderate level of consensus-based agreement).

If channelopathy as an aetiology for the seizures is suspected because of clinical or EEG features, then a sodium channel blocker should be used as a second-line ASM. This should be phenytoin or carbamazepine depending on the clinical state of the neonate (critically ill or otherwise well baby) and the regional availability of ASM and monitoring of drug levels. - high level of consensus-based agreement



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In a neonate with cardiac disorder(s), levetiracetam may be preferred as a second-line ASM. – (moderate level of consensus-based agreement)

In the review by ILAE Task force, 3 RCTs were included.

One study¹² assessed second-line therapy in neonates with seizures persisting after either phenobarbital or phenytoin. Seizures were controlled with phenobarbital in 5/13 (39%) and phenytoin in 4/15 (27%) neonates. There was no difference in efficacy between phenobarbital and phenytoin as second-line treatment (RR 1.44; 95%CI 0.49-4.27), but the sample size was small.

A second study¹³ assessed second-line therapy in neonates with seizures persisting after either phenobarbital or levetiracetam. Seizures were controlled with phenobarbital in 20/37 (54%) and levetiracetam in 1/6 (17%) neonates. There was no difference in efficacy between phenobarbital and levetiracetam as second-line treatment (RR 0.31; 95%CI 0.05-1.89).

A third study¹⁷ assessed second-line therapy in neonates with seizures persisting after phenobarbital. Seizures were controlled with lidocaine in 3/5 and midazolam in 0/3. There was no significant difference in efficacy between lidocaine and midazolam as second-line treatment (RR 4.67; 95%CI 0.32-68.03), but the sample size was too small. Many studies did not address adverse events, while some studies indicated that no adverse events were observed.

7.2.4. Continuation of ASM

Following cessation of acute symptomatic seizures (electroclinical or electrographic), without evidence for neonatal onset epilepsy, antiseizure medications should be discontinued before discharge home, regardless of MRI or EEG findings. (high level of consensus-based agreement)

Studies included in the ILAE Task force recommendations reported that the risk of subsequent developmental delay, seizures recurrence, epilepsy, or neurologic impairment was not different in patients with ASM (mostly phenobarbital) discontinued prior to discharge or continued after discharge.



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As there was only insufficient evidence on duration of ASM from RCTs, expert opinion (80%) mostly agreed that ASM should usually be discontinued before discharge independently of the presence or absence of MRI abnormalities, and 80% completely or mostly agreed that following cessation of acute symptomatic seizures in a neonate, ASM should usually be discontinued before discharge independently of presence or absence of EEG background abnormalities.

A prospective, observational, multicentre comparative effectiveness study¹⁸ published after the task force review also indicated neurodevelopment and risk for post-neonatal epilepsy at age 24 months was not different among children with acute systematic neonatal seizures whose ASM was discontinued or maintained at hospital discharge.

7.2.5. Third line ASM

A trial of pyridoxine (add-on to antiseizure medication (ASM)) should be attempted in:

- Neonates presenting with clinical features or EEG characteristics suggestive of vitamin B6-dependent epilepsy.
- Neonates with seizures unresponsive to second-line ASM without an identified aetiology.
(high level of consensus-based agreement)

At least 6 independent genetic disorders have been found to interfere with the bioavailability of pyridoxine and pyridoxal 5'-phosphate (PLP), resulting in vitamin B6-dependent epilepsy. Neonates with vitamin B6-dependent epilepsy may initially present with features suggesting HIE or systemic manifestations including lactic acidosis and acute abdomen. The systematic literature review did not identify any RCT studies investigating the effect of pyridoxine or PLP on neonates with seizures. Typical features of seizure semiology (myoclonic jerks, spasms), abnormal movements (eye movements, grimacing) and EEG (burst-suppression, discontinuity) have been described. Whilst some neonates with vitamin B6-dependent epilepsy respond immediately to pharmacological doses of pyridoxine or PLP, delayed responses are described and therefore treatment with pyridoxine or PLP should be continued for at least 3-5 days before concluding that it is not effective. Adverse effects of pyridoxine and pyridoxal 5'-phosphate included acute respiratory depression, depression of EEG amplitude, peripheral neuropathy.

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In the Delphi process, 100% completely or mostly agreed that a trial of pyridoxine (add-on to ASM) should be performed in a neonate or infant presenting with clinical features or EEG characteristics suggestive of vitamin B6 dependent epilepsy, and 96% completely or mostly agreed a trial of pyridoxine (add-on to ASM) should be attempted in all neonates with seizures without an identified aetiology not responding to second-line ASM. The risk of apnoea should be considered when a trial of pyridoxine is attempted. If vitamin B6-dependent epilepsy is suspected, following an unsuccessful trial of pyridoxine, PLP treatment may be tried even though this product is not licensed as medication. If those metabolic disorders are suspected, treatment should not be delayed, as a therapeutic trial with either pyridoxine or PLP can be started before diagnostic samples are collected as this does not affect the results.

7.2.6. Initiation

- Uncertainty exists over when to commence ASM
- It is generally agreed that rare brief seizures may not require treatment but should initiate EEG monitoring so the seizure burden can be evaluated.
- A seizure burden of >30-60 s per hour is considered as an indication to start treatment. Presence or absence of clinical signs should not impact treatment approach.
- Because of 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 electro-clinical seizures.
- Ideally neurophysiological monitoring should be commenced before anticonvulsants are administered, unless the infant is cardio-respiratory compromised by the seizure, as many ASM will alter the background activity of the EEG making subsequent neurophysiological assessment difficult.
- Phenobarbital is the first line ASM.
- If not responding to first-line ASM, phenytoin, levetiracetam, midazolam, or lidocaine may be used as a second-line treatment
- In a neonate with cardiac disorder(s), levetiracetam may be preferred as a second-line ASM.
- If channelopathy (e.g. KCNQ2/KCNQ3, SCN2A (early-onset), SCN8A) is suspected, then a sodium channel blocker (Phenytoin or carbamazepine) should be used as a first and

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second-line ASM. (clues: family history of neonatal seizures, onset day 2-7, otherwise well baby, tonic or sequential seizures with autonomic features)

- Consider a trial of pyridoxine in all neonates with seizures unresponsive to second line ASM without an identified cause (e.g. HIE/stroke) or with suggestive EEG patterns (e.g. burst suppression), even if not classically diagnosed with B6-responsive epilepsy.
- If no response to pyridoxine, pyridoxal-5-phosphate (PLP) should be trialed.

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.

7.2.7. Administration

Administer ASM:

- Intravenously to achieve rapid onset of action and more predictable blood levels.
- If there is no IV access and glucose and electrolyte abnormalities have been excluded, consideration should be given to intranasal or buccal midazolam.

7.2.8. Maintenance and duration of treatment

The duration of ASM should be as short as possible; however, this will depend on the diagnosis and the likelihood of seizure recurrence. If maintenance therapy is considered serum levels should be monitored (in drugs where an assay is available).

The ILAE 2023 consensus does not recommend prolonged maintenance unless there is a confirmed diagnosis of neonatal-onset epilepsy or recurrence after discontinuation

7.2.9. Cessation of treatment

Early withdrawal of ASM is supported in neonates with acute symptomatic seizures. Following cessation of acute symptomatic seizures (electroclinical or electrographic) without evidence for neonatal onset epilepsy, antiseizure medications should be ideally discontinued before discharge home, regardless of MRI or EEG findings.

7.3. ASM – specific drugs

7.3.1. Intranasal/buccal Midazolam

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

7.3.2. Phenobarbital (phenobarbitone)

- Preferred first line anti-seizure medication
- *Loading dose:* 20 mg/kg IV as a loading dose slowly over 20 minutes.
- *Second loading dose* of 10-20 mg/kg IV if baby continues to have seizures (max. total dose 40mg/kg). Respiratory support should be available if second dose is given
Maintenance dose: 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). If administered enterally then an alcohol-free solution must be used.
- *Therapeutic range:* Measure trough levels if on maintenance dose
Aim for therapeutic levels of 20–40 micrograms/ml (90-160micromols/l). Phenobarbital has a long half-life (2-4 days) in neonates and levels can take a long time to stabilise or come down. Renal and hepatic excretion can be affected in HIE. Drowsiness is common, especially if levels exceed 50mg/L, and respiratory depression becomes more likely.
- *Common adverse effects:* Respiratory depression, somnolence, depressed consciousness and poor feeding and hypotension.

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- *Note:* shown to be effective in less than 50%; clinical seizures may not be apparent after phenobarbital, however, electrical seizures could still persist (electro clinical uncoupling).

If no response to phenobarbital – Second Line ASM: phenytoin, levetiracetam, midazolam, or lidocaine may be considered

7.3.3. Levetiracetam

- *Loading dose:* 40 mg/kg IV over 15 minutes.
- *Second loading dose:* 20 mg/kg IV if required (**may be given after 20 mins**)
- *Maintenance:* 40-60 mg/kg/day IV/oral in 2 divided doses
- *Adverse effects:* Mild sedation, irritability
- *Note:* Usually well tolerated but limited information in neonatal population more info on levetiracetam neonatal pharmacokinetics is required.

7.3.4. Phenytoin

- *Loading dose:* 20mg/kg (slow IV infusion over 30 minutes)
- *Maintenance:* 5mg/kg/d IV/oral in 2 divided doses max per dose 7.5mg/kg
- *Therapeutic range:* measure trough levels 48 hours after IV loading dose.
Aim for therapeutic levels of 10-20 microgram/ml
- *Adverse effects:* infusion site irritation, necrosis, hypotonia, bradycardia, respiratory depression/arrest.
- *Note:* Phenytoin has poor oral bioavailability. Levels likely higher in infants receiving therapeutic hypothermia, thus adjust dosage according to local target levels. Cardiac monitoring required.
- If used for channelopathies, switch to carbamazepine for maintenance once oral administration is possible.
- IV phenytoin should ideally be administered via a large vein through an in-line filter (0.22 – 0.5 micron). Follow East of England parenteral monograph for details on dilution and administration.

Commented [GN1]: I know this is what the international guideline says, but Neonatal Formulary 9th edition and Evelina formulary has 12 hourly dosing. This is more usual and matches the regional IV monograph. Could we change to 12 hourly dosing??

These fairly recent papers
<https://jpppt.kglmeridian.com/view/journals/jppt/30/2/article-p170.xml>

<https://www.mdpi.com/2673-4087/7/1/8>

highlight more info on levetiracetam neonatal pharmacokinetics is required.
This would make a great study if anyone was interested in pursuing this with me 😊 ???

Commented [GN2]: I would suggest some cautionary advice with considering phenytoin as maintenance therapy. As it is very difficult to maintain a dose that has therapeutic effect because of rapidly changing pharmacokinetics in neonates.

I would suggest phenytoin maintenance is only used if there seizure failure with other agents.

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- *Cautionary advice* when considering phenytoin as maintenance therapy. It is very difficult to maintain a dose that has therapeutic effect because of rapidly changing pharmacokinetics in neonates. Consider phenytoin maintenance, ONLY if there is seizure failure with other agents.

7.3.5. Midazolam

- *Loading Dose:* 0.05-0.15 mg/kg (50 – 150 microgram/kg) as a slow IV injection over 5 minutes followed by a continuous infusion at 60 micrograms/kg/hour (1microgram/kg/min) increasing by 60 micrograms/kg/hour every 15 mins until seizures are controlled (max 300 micrograms/kg/hour).
- *Adverse events:* Respiratory depression, somnolence, depressed consciousness and poor feeding, hypotension
- Follow East of England parenteral monograph for details on standard concentrations of midazolam infusions that should be used.

7.3.6. Lidocaine (lignocaine)

- *Loading dose:* 2 mg/kg IV over 10 minutes
- *Maintenance:* 6 mg/kg/hour for 6 hours, reduce to 4mg/kg/hour for 12 hours, then reduce to 2 mg/kg/hour for 12 hours and stop. Preterm neonates may require lower doses. See chart below.

Normo-thermia	Loading phase		Maintenance phase 1	Maintenance phase 2
Weight	10 mins	4 hours	12 hours	12 hours
0.8–2kg	2 mg/kg	5 mg/kg/hr	2.5mg/kg/hr	1.25mg/kg/hr
2–2.5kg		6mg/kg/hr	3mg/kg/hr	1.5mg/kg/hr
>2.5–4.5kg		7mg/kg/hr	3.5mg/kg/hr	1.75mg/kg/hr

Hypo-thermia	Loading phase		Maintenance phase 1	Maintenance phase 2
Weight	10 mins	3.5 hours	12 hours	12 hours
2 – 2.5kg	2 mg/kg	6 mg/kg/hr	3mg/kg/hr	1.5mg/kg/hr
2.5-4.5kg		7 mg/kg/hr	3.5mg/kg/hr	1.75mg/kg/hr



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- *Adverse events:* Cardiac (arrhythmias, atrioventricular block, cardiac arrest), hypotension, methemoglobinaemia. Ensure continuous monitoring of heart rate, rhythm and blood pressure.
- *Notes:* Not to be given to a patient with congenital heart disease and/or on pro arrhythmic drugs such as phenytoin

Third line ASM

7.3.7. Pyridoxine hydrochloride

- *Loading dose:* 100 mg IV/oral followed by 30 mg/kg/d IV or orally in 2 divided doses for 3-5 days
- *Adverse events:* Respiratory depression, hypotension, prolonged treatment with high dosages may cause peripheral neuropathy.
- Ventilatory support should be available when loading dose is administered
- If effective continue until genetic results are available

7.3.8. Pyridoxal-5-phosphate

- *Dose:* 30mg/kg/d orally (no IV preparation available) in three divided doses for 3-5 days. 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.
- *Adverse events:* Respiratory depression, hepatotoxic, cirrhosis on prolonged use.
- Sudden respiratory arrest and profound hypotension may occur with the use of Pyridoxal 5 Phosphate. It is therefore advisable that any trial of Pyridoxal 5 Phosphate be started during working hours. Resuscitation facilities must be close at hand and intensive care facilities must be available.
- Initial patient monitoring required including baseline observations and continuous cardiac and saturation monitoring. Blood pressure, pulse, respirations and oxygen saturation should be monitored and recorded every 15 minutes for 2 – 3 hours following administration of Pyridoxal 5 Phosphate dose.
- *Note:* Not a licenced medical product.
- If effective continue until genetic results available

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If there is a strong family history or clinical background of channelopathies consider Phenytoin or carbamazepine.

7.3.9. Carbamazepine

- *Dose*: start with 2.5mg/kg 12 hourly and increase in increments of 2.5 - 5mg/kg every 3 days.
- In some cases of dose of 20mg/kg/day in 2 divided doses may be needed
- *Adverse events*: transient somnolence gastrointestinal symptoms, hyponatraemia, skin reactions
- Usually well tolerated but limited information regarding dosing and adverse effects in neonates.
- The MHRA and Novartis Pharmaceuticals issued guidance in 2025 that Carbamazepine liquid 100mg/5mL is no longer recommended for neonates below 4 weeks of age or below 44 weeks post-menstrual age, due to the amount of propylene glycol in the formulation

8. 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. In the prospective Neonatal Seizure Registry cohort, 13% developed post-neonatal epilepsy by 24 months (median onset 7 months); risk was higher with severely abnormal EEG background, ≥ 3 days of EEG seizures and abnormal neurological examination at discharge¹⁹. Risk is much higher in neonatal-onset epilepsies/DEE.

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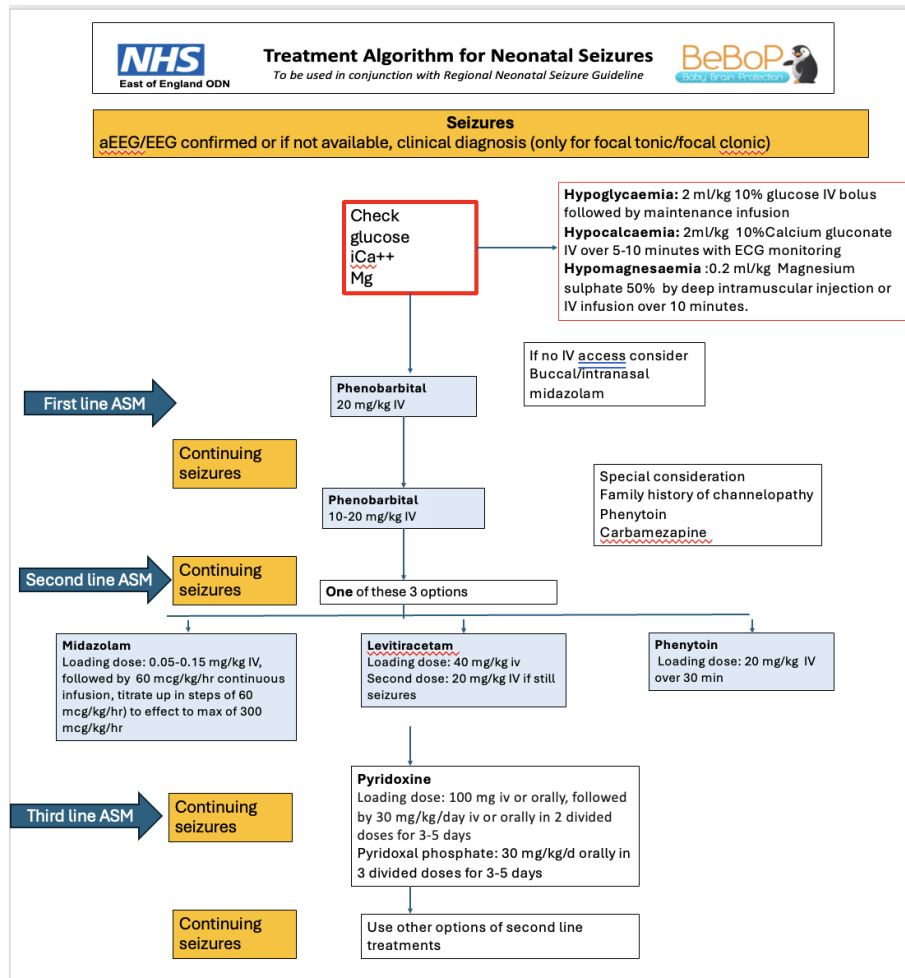
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Appendix 1





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Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

Details of person completing the form:	
Title:	Organisation:
First name:	Email contact address:
Surname:	Telephone contact number:
Title of document to be excepted from:	
Rationale why Trust is unable to adhere to the document:	
Signature of speciality Clinical Lead:	Signature of Trust Nursing / Medical Director:
Date:	Date:
Hard Copy Received by ODN (date and sign):	Date acknowledgement receipt sent out:

Please email form to: kelly.hart5@nhs.net requesting receipt.

Send hard signed copy to: Kelly Hart
Project Support/Office Manager
Box 402, Rosie Hospital,
Cambridge University Hospitals NHS Foundation Trust
Robinson Way, Cambridge. CB2 0SW