Queensland Clinical Guidelines

Translating evidence into best clinical practice

Maternity and Neonatal **Clinical Guideline**

Neonatal seizures V4

Queensland Government

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Cultural acknowledgement

We acknowledge the Traditional Custodians of the land on which we work and pay our respect to the Aboriginal and Torres Strait Islander Elders past, present and emerging.

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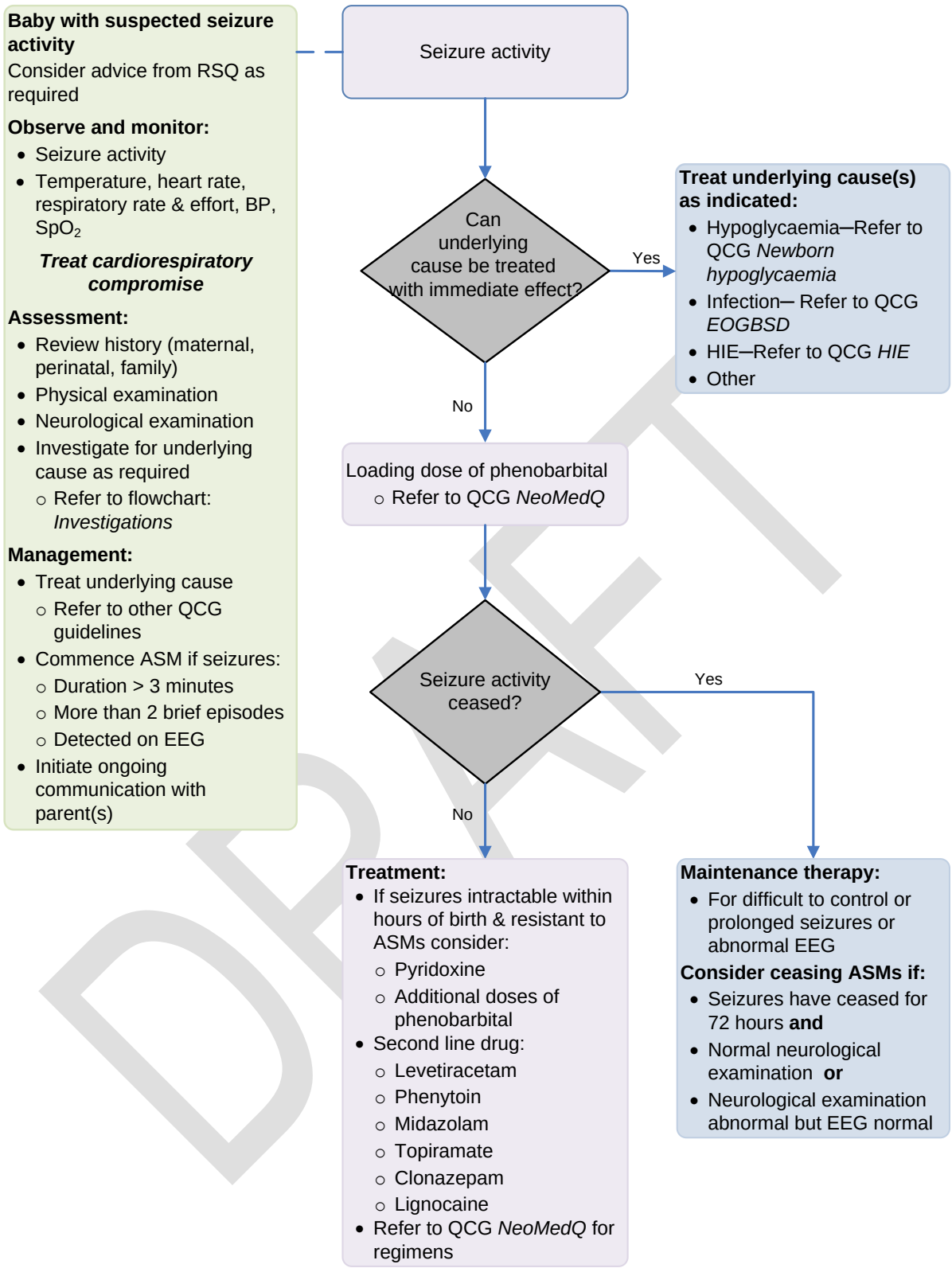
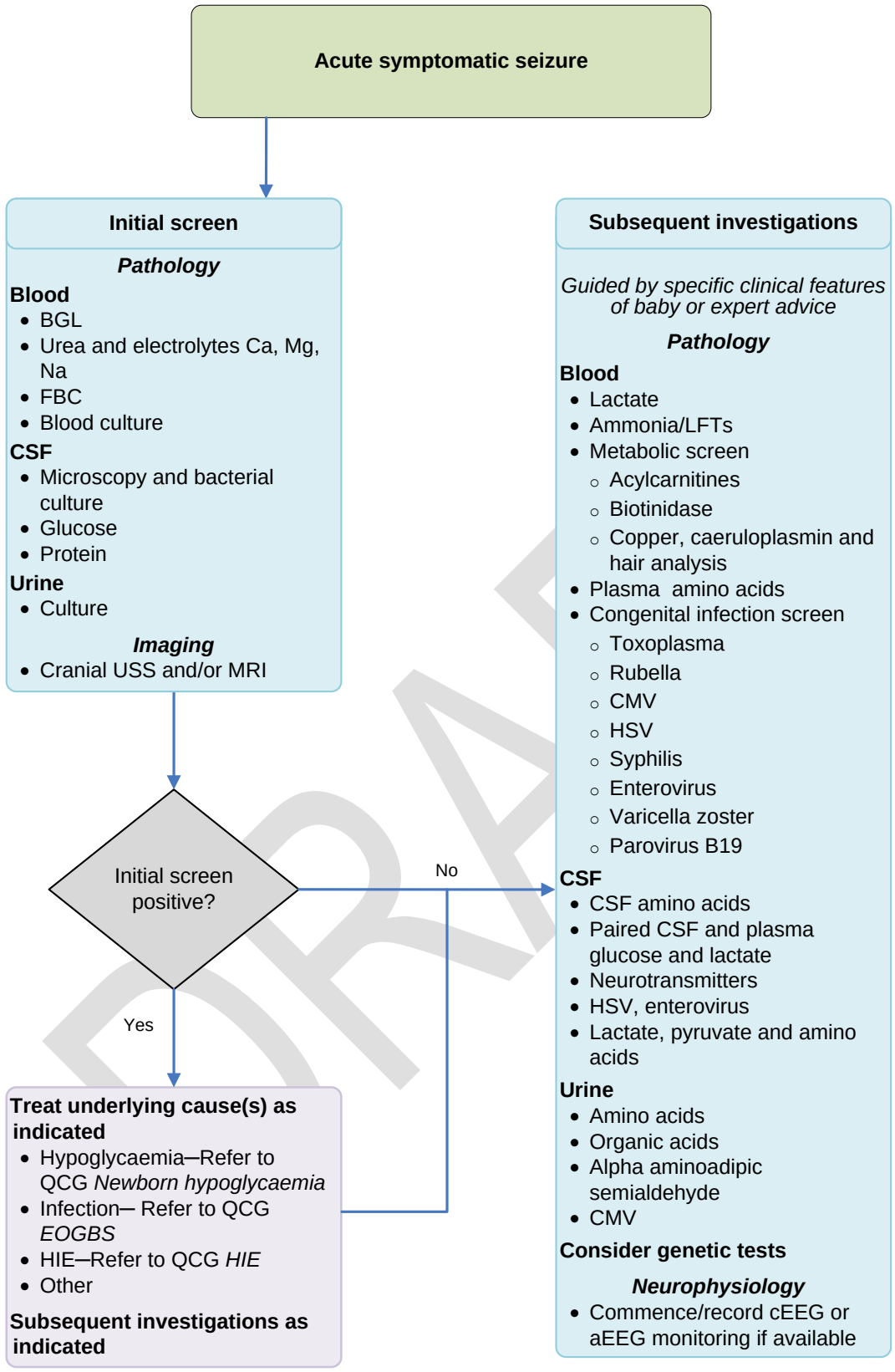
Flow Chart: Assessment and management of neonatal seizures



ASM: anti-seizure medications(s); **BP:** blood pressure; **EEG:** electroencephalogram; **EOGBSD:** early onset Group B Streptococcal disease; **HIE:** hypoxic ischaemic encephalopathy; **IV:** intravenous; **QCG:** Queensland Clinical Guidelines, **RSQ,** Retrieval Services Queensland, **>:** greater than

Flowchart: F22.23-1-V2-R27

Flow Chart: Investigations for neonatal seizures



BGL: blood glucose level, **CMV:** cytomegalovirus, **CSF:** cerebrospinal fluid, **EEG:** electroencephalogram, **EOGBSD:** early onset Group B Streptococcal disease, **FBC:** full blood count, **HIE:** hypoxic ischaemic encephalopathy, **HSV:** herpes simplex virus, **LFT:** liver function tests, **MRI:** magnetic resonance imaging, **NBST:** newborn bloodspot screening test, **QCG:** Queensland Clinical Guidelines, **SpO2:** peripheral capillary oxygen saturation, **TBR:** Total bilirubin, **TORCH:** toxoplasmosis, other (syphilis), rubella, cytomegalovirus,

Flowchart: F22.23-2-V2R27

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Abbreviations

aEEG	Amplitude integrated electro-encephalogram
ASM	Antiseizure medication
BGL	Blood glucose level
BP	Blood pressure
cEEG	Continuous electro-encephalogram
CNS	Central nervous system
CSF	Cerebro-spinal fluid
EEG	Electroencephalogram
GMA	General movements assessment
HIE	Hypoxic-ischaemic encephalopathy
HSV	Herpes simplex virus
MRI	Magnetic resonance imaging
msec	Millisecond
IM	Intramuscular
IV	Intravenous
TORCH	Toxoplasmosis, other (syphilis), rubella, cytomegalovirus, Herpes simplex
USS	Ultrasound scan

Definitions

Apoptosis	Process of programmed cell death[1]
Hydrocephalus ex-vacuo	Increased cerebro spinal fluid (CSF) volume but normal pressure when there is shrinkage of brain substance following damage to the brain caused by stroke or injury[2]
Holoprosencephaly	Brain malformation resulting in varying degrees of lack of separation of the cerebral hemispheres.[3]
Hydranencephaly	Non-viable anomaly where there are no cerebral hemispheres and the cranium is filled with cerebro spinal fluid CSF)[4]
Hypsarrhythmia	Abnormal inter-ictal pattern with electroencephalogram (EEG) high amplitude and irregular waves and spikes with background of chaotic and disorganised activity[5]
Ictal	Relating to seizures[6]
Kindling	Progressively increasing response of a group of neurons when exposed to repetitive electrical stimulation[7]
Lissencephaly	Rare, gene-linked brain malformation where there is absence of normal convolutions (folds) in the cerebral cortex and an abnormal, small head (although normal size at birth)[8]
Polymicrogyria	Abnormal development of the brain before birth characterised by too many folds (gyri) that are unusually small[9]
Schizencephaly	A rare congenital anomaly where unilateral or bilateral clefts in the cerebral hemispheres develop that may be filled with cerebrospinal fluid[10]
Spasticity	Muscular hypertonicity with increased resistance to stretch[11]
Seizure burden	Ictal (seizure) EEG activity expressed as summed electrographic seizure seconds within a given period of EEG recording[12]

1 Introduction

Seizures are sudden paroxysmal and abnormal alterations in electrographic activity, and are a sign of neurological dysfunction.[13,14] They are a neurological emergency that are difficult to diagnose and treat.[15]

Neonates are at especially high risk of seizures compared to other age groups.[15] The clinical presentation of neonatal seizures is variable, and clinical features are often absent or non-specific.[14] This has led to under-diagnosis and occasional over-diagnosis.[16,17]

The majority of seizures demonstrated on video electroencephalogram (EEG) monitoring do not have overt clinical signs.[15] Newborn babies can have movements that can be mistaken for seizures, where the EEG is normal.[17]

1.1 Context

Table 1. Context

Aspect	Consideration

Background	• Seizures occur more frequently in neonatal period than any other time
	• Higher incidence in preterm babies, especially lower gestational age and birth weight
	  ○ Due to associated morbidity of cerebral insults (e.g. intraventricular haemorrhage, periventricular leucomalacia)
	• Hypoxic ischaemic encephalopathy (HIE) and intraventricular haemorrhage (stroke) result in largest seizure burden[18]
	• Seizures can be associated with greater risk of long term neurodevelopmental disabilities[14,16]
	• Both clinical and electrographic seizures are associated with neurological sequalae including:
	  ○ Motor and cognitive deficits
	  ○ Increased risk of epilepsy in later life[16]

Incidence	• Generally,
	  ○ Term babies: 1–5/1000 live births[14,16,19]
	  ○ Preterm babies: 10–15/ 1000[16]
	• Birth weight:
	  ○ 1500–2500: 4.4/1000 live births
	  ○ Less than 1500 grams: 55–130/1000 live births
	  ○ Less than 1000 grams: up to 64/1000 live births[20]
	• Babies with HIE: 50–60%[21]

Clinical standards	• Document seizure date, time, duration and description on dedicated seizure form [refer to Table 11.History and examination] • Refer to Queensland Clinical Guideline *Standard care*[22]for care considered 'usual' or 'standard' ○ Includes for example: privacy, consent, decision making, sensitive communication, medication administration, staff education and support, culturally appropriate care

Referral	• Consider:
	  ○ Early discussion with neonatologist by contacting Retrieval Services Queensland (RSQ) regarding assessment, diagnosis and potential for transfer to a higher level nursery
	  ○ Telehealth
	• Refer to Queensland Clinical Guideline *Neonatal stabilisation for retrieval*[23]

2 Aetiology

Seizures occur when excessive and synchronised depolarisation occurs in a large group of neurons.[24] Most neonatal seizures occur in the context of a diagnosable underlying condition.[25] The reasons are multifactorial, and reflect different pre-, peri-, or postnatal disorders of the central nervous system (CNS).They include relative excitability of the developing neonatal brain[15] and high risk for brain injury

2.1 CNS causes

Table 2. CNS causes

Cause	Comment
Hypoxic-ischaemic[13,26]	• Most common cause of seizures in term babies[21,27,28]although clinical features may differ with gestational age[29] • Usually present before 24 hours of age and during rewarming period[21] • May be clonic or myoclonic seizures • Results from excessive depolarisation caused by a disruption to the adenosine triphosphate (ATP)-dependent pump[21] • Refer to Queensland Clinical Guideline *Hypoxic-ischaemic encephalopathy*[30]

Infection of CNS[25]	• Acute infection requires urgent investigation and consideration of treatment pending results[21,31,32]
	• Congenital infections may also require urgent investigation and treatment if suspected active infection
	• Consider HSV, CMV, Toxoplasmosis, Syphilis (*Treponema pallidum*), Varicella zoster, Parvovirus B19, Rubella[33]
	• Urgently investigate for:
	  ○ Bacterial meningitis[13,15] (consider *Escherichia coli* and *Streptococcus agalactiae* (Group B Streptococcus) and Listeria monocytogenes)
	  ▪ Septicaemia without meningitis may also result in seizures[34]
	  ○ Encephalitis—causes include:
	  ▪ Viruses[13,15] (e.g. herpes simplex (HSV), enterovirus, cytomegalovirus (CMV)
	  ▪ Parasites such as *Toxoplasma gondii* or
	• Bacterial pathogens[34] (e.g. *Escherichia coli* and *Streptococcus pneumoniae*)

Intracranial haemorrhage [13,25,35]	• Second most common cause of neonatal seizures[21] • Includes birth related head trauma[36] ○ Subgaleal haemorrhage[37] commonly presents 1–6 hours after birth[38] • Germinal matrix intraventricular haemorrhage (IVH) (more common in preterm babies especially born before 34 weeks gestation[39,40] • Subarachnoid and subdural haemorrhages (more common in term babies)[21]

Other cerebrovascular[25]	• Congenital vascular anomalies[21]
	• Thrombosis–associated with venous infarct[21]
	• Stroke[13]:
	  ○ Arterial
	  ○ Venous
	• Tend to present after 12 hours of age in otherwise well and alert baby[21]

2.2 Other causes

Table 3. Other causes

Cause	Comment
Biochemical/ metabolic[25]	• Hypoglycaemia[13,26,31] • Hypocalcaemia[13,31] • Hypomagnesaemia[13,31] • Hyponatraemia[13] • Hypernatraemia[13] • Urea cycle disturbances resulting in ammonia accumulation[13]

Inborn errors of metabolism[25]	• Rare inborn errors of metabolism including pyridoxine responsive seizures and other vitamin dependency[13,41]
	• Prepartum–may have maternal report of abnormal intrauterine movements (fluttering or hiccoughs)[42-44]
	• Myoclonic semiology–multifocal and generalised myoclonic jerks often intermixed with tonic signs, abnormal eye movement, grimacing or irritability
	• Associated with progressive clinical and EEG worsening–asymptomatic after birth and then clinical deterioration[21] usually seen after baby starts feeding[41]
	• Time of onset:
	  ○ Depends on the disorder:
	  ▪ Disorder resulting in key metabolite deficiency can present very early (e.g. pyridoxine dependent seizures)
	  ▪ Disorders resulting in accumulation of a toxic product may present late
	  ○ May also vary with severity and timing (e.g. hypoxia, infection)
	  ○ Associated with imaging showing prominent brain atrophy, apparent hypoxic-ischaemia injury without history of insult, or diffuse cerebral oedema
	  ○ Refractory to conventional treatment
	• Seizure activity may be accompanied by:
	  ○ Metabolic acidosis, electrolyte disturbance, abdominal distension, feed intolerance

Developmental/ congenital	• Abnormality of brain development[13] ○ Includes schizencephaly, lissencephaly, holoprosencephaly and hydranencephaly
Other	• Drug withdrawal or intoxication[45] • Refer to Queensland Clinical Guidelines *Perinatal substance use—neonatal*[46] and *Perinatal substance use—maternal*[47]

2.2.1 Other genetic epilepsies

Self-limiting (benign) neonatal seizure syndromes[13] including self-limited neonatal epilepsy and self-limited familial neonatal epilepsy. Suspect a severe neonatal epilepsy syndrome in newborn babies when there is no obvious cause for acute seizures. These are often associated with refractory seizures and poor neurodevelopmental outcomes.[45]

Table 4. Other genetic epilepsies

Cause	Comment
Self-limited neonatal epilepsy[45,48]	• Result from gene mutation • May have no specific aetiology • No family history of seizures • Usually normal history of pregnancy, labour and birth • Affects term and late term babies • Present within first few days to one week of age within a 24–48 hour time period • Brief (one to three minutes), unifocal clonic most common (may be associated with apnoea) • Normal pathology and imaging (e.g. metabolic studies, CSF, neuroimaging)Interictal EEG normal • Remit within first few weeks to months and are associated with good neurological outcomes

Self-limited familial neonatal epilepsy[12,45,48,49]	• One of several epileptic disorders caused by pathogenic variants in voltage-gate potassium channel genes (KCNQ2 and KCNQ3)
	  ○ Also associated with KCNQ3 and SCN2A
	• Family history of epilepsy
	  ○ May be no family history of epilepsy due undetected variants or may be variants more commonly associated with later onset of seizures
	• Typically occur within first 5-7 days
	• Focal or multifocal; clonic or tonic seizures
	• No other neurological abnormalities
	• Brief and resolve spontaneously
	• Interictal EEG normal
	• May continue to 2–3 months of age

Severe syndromes[45,49]	• A range of other genetic disorders causing epilepsy syndromes (e.g. early onset epileptic encephalopathy; Ohtahara syndrome) • Includes pathogenic variants of KCNQ2 and KCNQ2 developmental and epileptic encephalopathy • May be familial history of early myoclonic encephalopathy • Present in first week of life usually within hours of birth as segmental, fragmentary or erratic myoclonic • Early myoclonic encephalopathy is characterised by random, asynchronous twitching of limb muscles, followed by focal clonic seizures and repetitive tonic spasms • If gain of function KCNQ2 variant–startle like myoclonus, encephalopathy and abnormal EEG • Abnormal neurological examination–encephalopathy, hypotonia, lack of visual attentiveness • Abnormal EEG • Subtle abnormalities on brain MRI • Usually severe and refractory to treatment and result in neurodevelopmental disabilities

2.3 Presentation

Neonatal seizures evolve over time. The peak incidence occurs between 12 and 24 hours of age, but the time of onset is dependent on aetiology and treatment. Often the seizures cease by 72 hours of age.[50] The typical time of presentation is identified in Table 5. Presentation, but the day of onset may be variable.

Table 5. Presentation

Typical onset	Cause

Day 1[21,24,40,51,52]	• HIE (usually 4-48 hours of age)
	• Traumatic brain injury:
	  ○ Haemorrhage—subarachnoid (less than day 5), intraventricular, intracerebral
	  ○ Subdural haematoma (less than 24 hours of age)
	  ○ Sub-galeal
	• Stroke (arterial)
	• Infection (any time):
	  ○ Viral (HIV and HSV by day 7)
	  ○ Bacterial
	• Hypoglycaemia
	  ○ Preterm baby
	  ○ Small for gestational age
	  ○ Maternal gestational diabetes
	  ○ Polycythaemia
	• Severe neurometabolic disorders:
	  ○ Sulphite oxidase deficiency
	  ○ Non-ketotic hyperglycinaemia
	  ○ Urea cycle defects
	• Drug withdrawal syndromes
	• Pyridoxine dependent
	• Intoxication by local anaesthetic

Day 2[21,24,40,51,52]	• Intracranial haemorrhage
	• Stroke (venous thrombosis)
	• Glucose transporter deficiency
	• Electrolyte deficiency/disturbance (usually day 2–3):
	  ○ Hyponatremia
	  ○ Hypernatremia
	  ○ Hypocalcaemia
	  ○ Hypomagnesaemia
	• Infection
	• Self-limited familial and non-familial neonatal epilepsies

Day 3[21,24,40,51,52]	• Neurometabolic disorders
	• Cerebral malformations (usually before day 5):
	  ○ Lissencephaly
	  ○ Polymicrogyria
	  ○ Schizencephaly
	• Other genetic abnormalities
	• Infection
	• Hyperbilirubinaemia

3 Seizure description

Clinically a seizure is a paroxysmal alteration in neurological function.[13,31] Seizures can have motor manifestations, or little or no behavioural manifestations.[53] Underlying the clinical manifestation is an electrographic seizure.[14] Normal paroxysmal neonatal behaviours and movements, (e.g. myoclonus during sleep, nonconjugate eye movements and sucking without associated eye abnormalities) can be difficult to distinguish from pathologic conditions and epileptic seizures that may have subtle manifestations.[14]

3.1 Classification

Neonatal seizures are either electro-clinical or electrographical.[12,31]
Neonatal seizures:

- Considered focal at onset[36]
  - Involves one part of the brain and affecting one side of the body[53]
  - Asynchronous and migratory
- Rarely generalised onset–may be seen in some rare conditions (e.g. inborn errors of metabolism)[36]
- Described according to predominant clinical feature–motor, non-motor, sequential[36]
- Motor–automatisms, clonic, epileptic spasms, myoclonic and tonic[14,36]
- Non-motor–autonomic and behavioural arrest[14,36]
- Sequential–seizure type events with a sequence of clinical signs and EEG changes evident at different times[36]
- Unclassified–inadequate or unusual clinical features to classify[36]

3.2 Clinical presentation

3.2.1 Motor presentation

Table 6 Seizure description–motor presentation

Motor presentation		
Type	**Description**	**Comment**
Automatism[14,32,36]	• Co-ordinated motor activity usually when there is impaired cognition (e.g. HIE, preterm)–typically oral • Ocular–tonic horizontal eye deviation, or sustained eye opening with ocular fixation or cycle fluttering • Oral-facial-lingual movements–chewing movements, tongue thrusting, lip smacking • Limb movements–cycling, paddling, boxing jabs	• More common in term babies but also identified with preterm babies ○ Apnoeic spells • Are a rare manifestation of seizures and usually without accompanying bradycardia (unless prolonged hypoxaemia) • Require EEG confirmation • May be unilateral, bilateral symmetrical, bilateral asymmetrical
Clonic[14,32,36]	• Recurrent rhythmic movements of same muscle group–jerking ○ Usually slow at a rate of one to three per second ○ Fast contraction phase followed by slow relaxation of muscle • May involve face, arms, legs or trunk	• More reliably diagnosed by clinical observation • More likely in babies who have: ○ Stroke cerebral haemorrhage ○ HIE • Primarily occur in term babies • May be: ○ Focal, multifocal or bilateral ○ Symmetric or asymmetrical
Myoclonic[14,32,36]	• Non-rhythmical, random, sudden brief (less than 100 msec) involuntary single or multiple contractions of muscles or muscle groups–typically not repetitive or may recur at a slow rate • Tendency to affect flexor muscles or muscle groups–variable topography (axial, proximal limb, distal) • More likely to have EEG changes ○ Include burst suppression, focal sharp waves and hypsarrhythmia	• More likely in babies who: ○ Are preterm ○ Have inborn error of metabolism • Difficult to differentiate from non-epileptic myoclonus without EEG • Occur rarely but carry worst prognosis • May be: ○ Focal, multifocal ○ Bilateral asymmetric ○ Bilateral symmetric
Tonic[14,32,36]	• Sustained increase in muscle contraction–lasts a few seconds to minutes • Generalised ○ Tonic extension (resemble decerebrate posturing) or ○ Tonic flexion of arms and extension of legs (mimics decorticate posturing) ○ May involve one extremity or whole body axial musculature in a opisthotonic fashion • Focal involves one extremity and especially associated with eye deviation	• Rare–developmental and epileptic encephalopathy • More common in preterm babies who have poorer prognosis ○ Presumed pathophysiology is non-epileptic • Cannot be provoked by stimulation or suppressed by restraint • May be: ○ Focal, unilateral ○ Bilateral asymmetric, bilateral symmetric

3.2.2 Non-motor and other presentation

Table 7. Seizure description–non-motor and other presentation

Type	Description	Comment
Epileptic spasm[36]	• Flexion of proximal and truncal muscles • More sustained than myoclonic movement, not as sustained as tonic seizure • May have grimacing, head nodding, subtle eye movements	• Motor presentation • Brief and rare in newborn babies • Seen in inborn errors of metabolism
Non-motor presentation		
Autonomic[36]	• Distinct alteration of autonomic nervous system function (cardiopulmonary, pupillary, gastrointestinal, sudomotor, vasomotor, thermoregulatory) • May present as apnoea	• Requires EEG • Rare in isolation • Seen in IVH, occipital or temporal lobe lesions
Behavioural arrest[36]	• Pause in activities/immobilisation	• Require EEG confirmation
Sequential presentation		

Sequential seizure[36]	• Several seizure manifestations occurring in sequence (not necessarily simultaneously) in a given seizure
	• Sequence of signs, symptoms and EEG changes
	  ○ May manifest as tonic, clonic, automatisms, and autonomic features (including apnoea)
	  ○ Show varying lateralisation during single seizure
		• Often seen in genetic epilepsies

Unclassified		
Unclassified seizure type[36]	• Inadequate information or unusual clinical features • Unable to classify	• Diagnosed from EEG/aEEG

3.4 Non seizure activity in babies

Table 8. Non-seizure activity

Aspect	Comment
Jitteriness[54,55]	• Generalised, short duration very rapid tremulous movements • Recurrent and symmetrical tremulousness of all limbs or just one limb • Does not affect the face and not associated with eye deviation or autonomic change • Commonly seen in many of the same conditions that are associated with neonatal seizures and more commonly are associated with neuronal hyperactivity, (e.g. drug withdrawal (from HIE, maternal drug ingestion), hypocalcaemia, and hypoglycaemia) • Reducible by tactile stimuli, gentle passive flexion of the limb or physical restraint (by holding the baby) ○ Also lacks associated features, (e.g. tachycardia or apnoea) • May also have a pathological basis • If associated with perinatal complications, risk of adverse perinatal outcomes
Excessive startles[52,55,56]	• Markedly excessive startles relative to the stimulation, (e.g. auditory, touch and tonic stiffening) • Can be a sign of an encephalopathy and also seen in hyperekplexia • Can be stopped by flexion of the forehead to the chest
Benign neonatal sleep myoclonus[52,54-58]	• Benign condition in which the infant has myoclonic jerks during sleep • Involves one or more limbs–more commonly observed in arms • Limb movements in slow wave sleep often just after falling asleep or waking up, and can occur in rapid succession • Focal or bilateral fast rhythmic myoclonic jerks • Can be quite dramatic–whole body may shake ○ Ceases immediately when the baby awakens • May worsen if baby is held
Tremor[56,58]	• Involuntary generalised movement • Rhythmical oscillating around a fixed axis • If pathological related to underlying condition, (e.g. HIE, intracranial haemorrhage, hypoglycaemia, sepsis, drug withdrawal)
Clonus[56,59,60]	• Rhythmical oscillating stretch reflex–involuntary muscle contractions and relaxation in muscle around a joint • Can be stopped by change of position of joint • Can be provoked by quick movements of joint, e.g. ankle dorsiflexion • Repetitive muscle contraction can be normal • If abnormal amount of clonus, suspect upper motor neuron lesion
Hyperekplexia[54,58]	• Rare genetic disease also known as startle disease • General stiffness while awake, nocturnal myoclonus and an exaggerated startle reflex • Hypertonia or tonic spasms occur on awakening or from auditory or tactile stimuli • If severe may interfere with breathing

3.4.1 Jitteriness versus seizures

Table 9. Jitteriness versus seizures

Clinical feature[52]	Jitteriness	Seizure
Abnormal gaze or eye movement	No	Yes
Predominant movement	Tremor, rapid, oscillatory	Clonic, jerking, tonic
Movements cease with passive flexion	Yes	No
Stimulus provoked movements	Yes	No
Conscious state/ autonomic change	Awake or asleep/no change	Altered

4 Diagnosis and management

Seizures can be difficult to diagnose. The differential diagnosis for neonatal seizures is broad and includes encephalopathic, structural, metabolic, infections and genetic causes.[31] Recurrent and prolonged seizures are harmful to the developing brain, and require rapid recognition and assessment[13,16] to identify and treat underlying causes, prevent further brain injury and stop seizure activity.

Abnormal movements in the newborn baby may either be seizure activity (with seizures shown on an EEG), or simply abnormal movements without electrographic evidence of a seizure.[61]However, electrographical seizures may not be associated with abnormal movements or other clinical correlate.[15,40] Approximately one third of neonatal seizures clinically correlate with simultaneous video EEG recordings.

4.1 Initial management

Table 10. Initial assessment and management

Aspect	Comment/good practice point

Resuscitation	• Establish adequate airway, ventilation and perfusion[15,62-64]
	  ○ Minimise additional postnatal hypoxaemia and hyper- or hypocapnia
	• Commence cardio-respiratory, oxygen saturation and blood pressure monitoring in babies:
	  ○ At risk of encephalopathy including alterations in autonomic functioning which may be indicative of seizure activity
	  ○ Being administered antiseizure medication (ASM)
	• Obtain umbilical venous (UV) or intravenous (IV) access
	• Refer to Queensland Clinical Guideline *Neonatal resuscitation*[65]

Assessment/ examination	• Undertake comprehensive history and assessment of baby: ○ Refer to Table 11. and Table 13. Initial investigations

Treat underlying causes	• HIE[15]–refer to Queensland Clinical Guideline *Hypoxic-ischaemic encephalopathy*[30]
	• Biochemical causes e.g. hypoglycaemia[15] [refer to Queensland Clinical Guideline *Newborn hypoglycaemia*[66]]
	• Suspected bacterial infection according to local protocols or with empirical antibiotic therapy
	  ○ Commence:
	  ▪ Benzyl penicillin IV **AND** gentamicin IV **OR**
	  ▪ Amoxicillin/ampicillin IV **AND** gentamicin IV **AND**
	  ▪ If bacterial meningitis is suspected, **ALSO** commence cefotaxime IV
	  ○ Refer to Queensland Clinical Guidelines *NeoMedQ Benzylpenicillin*[67], *Gentamicin*[68], *Ampicillin*[69], and *Amoxicillin*[70]
	• Commence acyclovir IV until cerebrospinal fluid (CSF) PCR for herpes simplex virus (HSV) is known to be negative
	  ○ Refer to Queensland Clinical Guidelines *NeoMedQ Aciclovir*[71]
	• In the absence of hypoglycaemia commence ASM[64]
	• Treat other common biochemical derangements[15] such as:
	  ○ Hypocalcaemia–with 10% calcium gluconate IV
	  ▪ Refer to Queensland Clinical Guidelines *NeoMedQ Calcium gluconate 10%*[72]
	  ○ Hypomagnesaemia–with 50% magnesium sulphate
	  ▪ Refer to Queensland Clinical Guidelines NeoMedQ Magnesium sulphate[66]
	• If maternal substance use known or suspected, consider neonatal abstinence syndrome
	  ○ Refer to Queensland Clinical Guidelines *Perinatal substance use–neonatal*[46] and *Perinatal substance use–maternal*[47]

4.2 Assessment of baby

Table 11.History and examination

Aspect	Comment
History	• Maternal antenatal history including[13]: o Previous miscarriages o Gestational diabetes (causing neonatal hypoglycaemia) o Infections and any treatment received (including sexually transmitted disease) particularly HSV, syphilis, cytomegalovirus (CMV) and toxoplasmosis o Use of prescription and other substances (e.g. opioids, alcohol, serotonin-reuptake inhibitors (SSRI), serotonin-nonreuptake inhibitors (SNRI), benzodiazepines, barbiturates, amphetamines)[45] [refer to Queensland Clinical Guidelines *Perinatal substance use-maternal*[47] and *Perinatal substance use-neonatal*[46]] o Clotting or bleeding tendencies o Pre-eclampsia o Hiccoughing or fluttering in-utero as a clue to seizure activity usually when metabolic disorder is present[42,44] • Family history[13] of epilepsy especially maternal in infancy or other family members (consanguinity)[31] • Perinatal history including type of birth and resuscitation and any: o Fetal distress o Birth trauma o Perinatal asphyxia
Examination	• Physical examination[13,31] : o Congenital anomalies o Head circumference as microcephaly may be indicative of underlying brain malformation o Birthmarks o Somatic abnormalities o Facial dysmorphology • Refer to Queensland Clinical Guideline *Newborn baby assessment (routine)*[73] • Abnormal neurological examination e.g. abnormal mental status, level of alertness, spontaneous movement or tone)[13,31,52] o Refer to o Appendix B Abnormal neurological examination of term/near term baby • Signs of sepsis (e.g. bulging fontanelle caused by meningitis or rash suggestive of infection)[31] [refer to Queensland Clinical Guideline *Early onset Group B streptococcal disease*[74]
Observations	• Monitor and record vital signs[13] including heart rate, respiratory rate and effort, oxygen saturations, temperature, colour, blood pressure as indicated (e.g. if phenytoin administered) • Consider time of presentation of seizures[40] • Observe and record seizure activity[13] o Date, time and duration of any event o Whether seizures are stereotypical with clear onset and offset o Type of seizure activity o Abnormal eye movements o Progression of events o Autonomic changes (e.g. apnoea, hypotension, hypertension) o Any provoking stimuli (e.g. handling, noise) o Whether activity can be stopped or modified with posture or restraint o EEG correlate if concurrent monitoring in place • Document response to medications administered

4.3 EEG monitoring

Table 12. Clinical assessment

Aspect	Consideration

Context	• EEG is the gold standard[12,15,25]
	  ○ Well-established, non-invasive real time monitoring of brain activity and function including functional brain abnormalities[75]
	  ○ Provides accurate diagnosis of seizures
	  ○ Identifies area of seizure origin in brain
	  ○ Determine frequency, duration and propagation[76]
	• Has prognostic value–identifies babies at risk of abnormal outcome

Monitoring	• Commence continuous EEG monitoring if available[13] to confirm clinical event is seizure activity[76] ○ Majority of electrographic seizures do not have any overt clinical signs[40,77] • More accurate than clinical observation alone, and most accurately interpreted with knowledge of medical history and overall clinical condition[76]

aEEG	• Amplitude integrated EEG (aEEG)[76]:
	  ○ Convenient bedside tool using limited number of channels[76]
	  ○ Useful also for monitoring background brain activity (e.g. identifying variability as a sign of neurological wellbeing)
	  ○ Lower sensitivity and specificity than continuous EGG (cEEG) for brief, focal seizures[62]
	  ○ Filtered, processed and displayed in time-compressed scale
	• Has prognostic value in assessing general neurological well-being

cEEG	• cEEG–conventional, prolonged, continuous video EEG ○ Recommended for babies at high risk for seizures and/or paroxysmal events[78]

Seizure diagnosis	• Seizures are diagnosed if EEG[14]:
	  ○ Spike is sudden and repetitive or
	  ○ Spikes are sharp and evolve in frequency, voltage morphology and/or location
	• Abnormal with repetitive and evolving pattern, voltage greater than 2 microvolts and duration greater than 10 seconds[12]

4.4 Investigations

Investigations are dependent on the individual baby and circumstances including the likely cause of the seizures. Consider the maternal history, and the baby's history including presentation and type of seizures, and response to treatment. Initial investigations are undertaken when a baby presents with neonatal seizures. Further investigations are stratified according to possible cause.

Table 13. Initial investigations

Aspect	Comment/good practice point
Blood[13,31,32,79]	• BGL • Urea, electrolytes including calcium and magnesium • Full blood count • Liver function tests (LFTs) and total bilirubin (TBR) • Blood cultures • Blood gas for pH and lactate • Newborn bloodspot screening test (NBST) • Toxoplasmosis, other (e.g. syphilis), rubella, cytomegalovirus, herpes simplex (TORCH)
CSF[13,31,79]	• If infection suspected: o Microscopy and bacterial culture o PCR (bacterial and viral), (e.g. HSV) o Glucose o Protein o Blood o Colour
Urine[61]	• If infection suspected –microscopy and culture
Imaging[31,32,40,55,61,80]	• Ultrasound scan (USS) for detection of intra-ventricular and parenchymal haemorrhage • Magnetic resonance imaging (MRI): o Optimal neuroimaging modality o Preferable to computed tomography or USS o Does not aid the diagnosis of seizures, but can be useful for diagnosing intracranial lesions associated with seizures o Greater sensitivity in identifying brain malformations, intracranial haemorrhage and ischaemic damage o Diagnostic for cerebral dysgenesis, lissencephaly and other neuronal migration disorders o Timing is dependent on suspected cause of seizures (e.g. as soon as possible for suspected brain malformation or serious intracranial haemorrhage and day 5–10 for baby with HIE [Refer to Queensland Clinical Guideline *Hypoxic-ischaemic encephalopathy (HIE)*[30] o Use if the aetiology is not identified and seizures resistant to usual ASMs

4.5 Subsequent investigations

Table 14. Subsequent investigations

Aspect	Comment
Context	• Guided by the baby's clinical features or expert opinion
Clinical[31]	• Pyridoxine test (if baby's seizures refractory and unresponsive to conventional ASM)

Blood[13,31,32,61]	• Lactate
	• Ammonia
	• Thrombophilia screen
	• Metabolic screen
	  ○ Acylcarnitine
	  ○ Biotinidase
	  ○ Copper, caeruloplasmin and hair analysis
	  ○ Amino acids

CSF[31,39]	• Amino acids • Neurotransmitters • HSV, enterovirus • Lactate, pyruvate and amino acids • Paired CSF and plasma glucose, lactate and pyruvate
Urine[13,31,39]	• Organic acids • Metabolic screen including ketones, reducing substances, amino acids • Alpha aminoadipic semialdehyde • CMV • Sulfites • Creatinine

Other[61]	• Congenital infection screen (in addition to initial TORCH screen)
	  ○ Enterovirus
	  ○ Varicella zoster
	  ○ Parovirus B19
	• Consider genetic tests

Neuroimaging[31]	• MRI spectroscopy with spectroscopy

4.6 Management and treatment

- The principles for acute symptomatic neonatal seizure management include[16,18,62]:
  - Rapid and accurate identification of seizures[16] clinically and where possible by EEG (not usually available during first clinical seizure)
    - Under treatment may lead to kindling of additional seizures, and add to existing brain injury and alter seizure thresholds in the brain[18,31]
    - Overtreatment results in exposure to neurotoxic medicines and prolonged intensive care with associated risks (e.g. separation from parents, complications from procedures, sedation)[18,31]
  - ASM management:
    - Appropriate for seizure type[16]
    - Titrated to stop electrographic seizures
    - Early discontinuation once seizures have ceased[50]
- Prevention of secondary problems by maintaining normal physiological temperature, blood glucose, oxygenation, ventilation and blood pressure[62]

4.7 Continuing care

Table 15. Continuing care

Aspect	Comment/good practice point
Medications	• Refer to Section 5 Medications

Model of care	• Provide family centred care
	• Establish early and ongoing communication with parents
	  ○ Repeat information as often as required
	• Discuss management plan and prognosis with honesty and sensitivity
	• Document discussions in medical record
	• Involve social worker to support parents and family
	  ○ Long term sequalae from the underlying cause of the seizures may have profound impact on quality of life for the baby and family

Parents	• Discuss baby's condition, and option for care and treatment with parents • Refer to 7.1 Discharge planning
Documentation	• Document any episode of unusual or stereotypical movement and alterations in autonomic functioning [refer to Table 11.] • Video (if available) abnormal movements simultaneously with recording of cardiorespiratory monitoring
Environment[81]	• Provide developmentally supportive care • Provide comfortable and supportive positioning • Reduce and manage pain and stress during procedures (e.g. analgesia, containment) • Reduce noise, light, invasive treatment and care activities

5 Medications

While pharmacological options for treatment of neonatal seizures have increased there is limited evidence regarding the optimal pharmacological treatment strategy.[16,32]Consider benefits and risks of available options including potential efficacy, potential toxicity and side effects, and anticipated rapidity of response.[82] Phenobarbital is recommended as the drug to be used. Due to an insufficient evidence base, there is variation in practice for the preferred medication(s) for second line treatment.

Table 16. Principles

Aspect	Comment/good practice point
Context	• Evidence based recommendations from randomised controlled trials (RCT) is lacking regarding the relative benefits versus the risk of harm from ASMs used to treat neonatal seizures[16,32] • Hypothermia and the re-warming phase of HIE management may alter ASM pharmokinetics[83] ○ Refer to Queensland Clinical Guideline *Hypoxic ischaemic encephalopathy (HIE)*[30]
Expert recommendation	• Treat both clinical and electro-clinical seizures as they have similar pathophysiology • Phenobarbital is the preferred first line medication[84] ○ Refer to Table 17. Phenobarbital

Principles	• Treating the underlying cause of the seizures is critical to prevent clinical deterioration, further brain damage and poor long term neuro-developmental outcomes[85]
	• Commence treatment when:
	  ○ Clinically apparent seizure lasts more than three minutes
	  ○ More than two briefer seizures occur
	  ○ Electroencephalographic seizures are present[80] lasting longer than 30–60 seconds regardless of the presence of absence of clinical signs[12]

Maintenance and duration of treatment	• Optimal duration of treatment with ASM is unknown
	• Consider discussion with Retrieval Services Queensland (RSQ) before introducing second line ASM
	• Duration of treatment considerations include[50]:
	  ○ Baby's neurological status
	  ○ EEG
	  ○ Underlying aetiology[86]
	• Cease ASM when free of seizures for 72 hours and neurological examination is normal[80,86]
	  ○ If ASM discontinued for babies after resolution of acute symptomatic seizures at time of hospital discharge there was no difference in functional neurodevelopment or epilepsy at 24 months of age[50]
	• Targeted maintenance treatment for genetic and metabolic disorders usually lifelong[80,86]
	• Treatment usually continued if there is known progress to epilepsy (e.g. structural brain malformations and neonatal epilepsy syndromes)

5.1 Anti-seizure medications

5.1.1 Phenobarbital and levetiracetam

Table 17. Phenobarbital and levetiracetam

Phenobarbital	

***Phenobarbital**	• First line treatment[26,87]
	• More effective treating neonatal seizures than levetiracetam[84,88]
	• A second line drug is often required
	  ○ Phenobarbital may be discontinued when there is a therapeutic level of the second line drug
	• If relevant, refer to Queensland Clinical Guideline *Hypoxic-ischaemic encephalopathy*[30]
	• Administer loading dose
	  ○ For refractory seizures administer additional doses
	• Maintenance:
	  ○ Commence only if seizures continue after the loading doses
	• Refer to NeoMedQ Phenobarbital[89]
	• Discontinue after three days from last seizure, if normal neurological examination, EEG and MRI[90]

***Levetiraetam**[84,87,91]	• Second line ASM for seizures refractory to phenobarbital • Not as effective as phenobarbital in treating neonatal seizures • Associated with lower risk of adverse events ○ Data regarding adverse effects in neonates is limited to case reports and abstracts • Loading dose not required but may be given if urgent seizure control required • Refer to NeoMedQ Levetiracetum[92]

5.1.2 Other ASM

Table 18. Other ASM

ASM	**Consideration**
***Phenytoin**	• Administer loading dose and commence maintenance: • Refer to NeoMedQ Phenytoin[93] [In Press]
***Midazolam**[94]	• Second line ASM for seizures refractory to phenobarbital • Seldom arrests EEG evidence of seizure activity if phenobarbital has not been successful • Refer to NeoMedQ Midazolam[95]
^Topiramate[61]	• May be considered as second line ASM for seizures refractory to phenobarbital • Refer to NeoMedQ Topiramate[96]
***Clonazepam**[97,98]	• Second line treatment for seizures ○ Drug of choice for hyperekplexia • Seldom arrests EEG evidence of seizure activity if phenobarbital has not been successful • Sedative effect may mask cortical seizure activity that has not been suppressed • Refer to NeoMedQ Clonazepam[99] [In Press]
***Lidocaine**[61]	• Used for severe recurrent or prolonged seizures not responding to first line treatment • Refer to NeoMedQ Lidocaine [100] [In Press]

*Refer to an Australian pharmacopoeia for complete drug information
^Not on List of Approved Medicines (LAM)in Queensland

5.2 Pyridoxine (vitamin B6) deficiency

Table 19. Pyridoxine

Pyridoxine (vitamin B6)	
Comment[48,98,101-103]	• Vitamin B6 is a required enzyme in the biosynthesis of dopamine and serotonin • Used for diagnosis and treatment of pyridoxine dependent seizures • Consider pyridoxine dependency in any baby with severe seizures even if there is a clear cause (e.g. birth asphyxia)

Diagnosis and treatment	• Classic presentation is intractable seizures that appear within hours of birth and are resistant to conventional ASM[104]
	  ○ Baby responds rapidly to IV pyridoxine[105]
	  ○ Seizure type[105,106]–focal, generalised, clonic, tonic, myoclonic jerks, infantile spasms, status epilepticus, febrile seizures, abnormal eye movements, grimacing or irritability
	  ○ Progress rapidly to status epilepticus
	• Neurologic symptoms (pre-treatment)–hypotonia, hypertonia, dystonia, tremors, strabism, irritability, lethargy, encephalopathy[106], hyperalertness, sleep disturbances
	• Systemic symptoms include bile stained vomiting, abdominal distension, poor feeding, hypotension, respiratory distress, macrocephaly[106]
	• Biochemical abnormalities in acute phase–hypoglycaemia, lactic acidosis, abnormal CSF and plasma amino acids[106]
	• Seizures may occur with or without ictal changes on the EEG[106]
	• Maternal report of rhythmic fetal movements inutero[42-44,105,106]
	• A pyridoxine level of less than 20 nanomoles/L is indicative of a deficiency[103]

Dose and administration	• Administer with expert advice
	  ○ Contact RSQ for discussion with a neonatologist
	• If responsive then commence maintenance therapy (required for life)[90]
	• Observe for bradycardia, apnoea, hypotension and hypotonia
	  ○ Monitor cardio-respiratory function
	  ○ Ventilator support may be necessary
	• Best administered while EEG monitoring, but absence of EEG should not delay administration
	• Refer to NeoMedQ Pyridoxine[107]

*Refer to an Australian pharmacopoeia for complete drug information

6 Ongoing care

6.1 Discharge planning

Document discussions with parents, including emergency seizure management at home, prognosis, follow-up and parental decisions to enable consistency of information. Provide the parents with appropriate discharge information and documentation including:

- A seizure emergency management plan[50]
- A copy of the discharge summary including the type of seizures and medications
- Contact details of available support services available in the local area or online[108]
- Copies of referrals to other services
- Follow up appointments

6.2 Follow up

Table 20. Follow up

Aspect	Comment/good practice point
Context[21,75]	• Preterm babies are at greater risk of poor neurodevelopmental outcomes • Follow up by multidisciplinary team to assess developmental outcomes • Depends on cause of seizures and response to treatment
Follow up care	• Facilitate follow up with verbal and written communication, and assistance with appointments as required • Consider: o General practitioner and child health nurse o Paediatrician in local area o If baby discharged home on ASMs paediatric neurologist or neonatologist according to local arrangements–if available telehealth may be used
Early intervention[21,109]	• Early intervention when the brain is most plastic minimises developmental disabilities • Consider multi-disciplinary team to identify any motor and cognitive deficits, and timely neuro-developmental early invention using simple tools such as the General Movements Assessment (GMA), parent screening and use of Ages and Stages questionnaire o Abnormal fidgety GMA at three months of age is predictive for cerebral palsy and other neurodevelopmental delay o GMA and has been validated in term (with HIE) and preterm babies as a predictor of cerebral palsy o GMA requires 15 minutes of observation of the baby by video and analysis by a trained observer in the fidgety movements stage (i.e. three months corrected age) • If underlying genetic aetiology of seizure consider geneticist follow up

6.3 Prognosis and outcomes

Table 21. Prognosis

Aspect	Comment
Prognosis [24,29,40,45,110]	• Neonatal seizures and seizure burden are associated with poor outcomes • The aetiology of seizures determines the outcomes and prognosis • Strongest predictors of outcome–underlying cause and background EEG activity • Tends to be worse for preterm babies as often associated with underlying brain injury

High risk of poor outcome [27,40,45,111,112]	• HIE
	• Prematurity especially those with most serious life threatening illnesses
	  ○ Early onset (within 48 hours of birth)
	  ○ Repeated seizures of greater than or equal to one hour in duration
	  ○ Recurrent seizures of greater than 48 hours
	• Cerebral dysgenesis
	• CNS infection
	• Severe IVH or intercranial haemorrhage
	• Severely abnormal EEG inter-ictal activity (isoelectric pattern, paroxysmal, burst-suppression and low voltage background)
	• Persistence of a diffuse EEG abnormality
	• More than one ASM to control seizures
	• Other factors:
	  ○ Severely abnormal neurological examination
	  ○ Severely abnormal neuroimaging
	  ○ High seizure burden
	  ○ Presence of status epilepticus

Associated with favourable outcome [20,109,113]	• Normal neurological examination
	• Normal MRI
	• Normal GMA at age 3 months
	• Focal clonic seizures
	  ○ Transient metabolic disturbance (e.g. hypocalcaemia)
	  ○ Focal lesions (brain haemorrhage or stroke) on MRI
	  ○ Lesion confined to relatively circumscribed areas of the brain
	• Brief or rarely reoccurring seizures
	• Normal inter-ictal EEG
	• Normal EEG within 24 hour of birth generally has good prognosis
	• Neonatal sleep myoclonus

6.3.1 Outcomes

Table 22. Outcomes

Aspect	Comment

Morbidity and mortality [24,27,29,40,77,113-116]	• Risk of acute effects and long term sequelae including long term morbidity and neonatal mortality
	• Acute and long term adverse effects result from energy failure, excitotoxicity, neuronal death, apoptosis and status epilepticus
	• Complications include cognitive, motor and behavioural problems:
	  ○ Neurodevelopmental disability (e.g. cerebral palsy, spasticity, learning difficulties, intellectual disability)
	  ○ Cerebral atrophy
	  ○ Hydrocephalus ex-vacuo
	  ○ Microcephaly
	  ○ Epilepsy
	  ○ Feeding difficulties
	  ○ Behavioural problems, (e.g. autism, attention deficit disorder)
	  ○ Cognitive dysfunction, (e.g. memory deficit)
	  ○ Headache

Predictors of outcome[45,112]	• Seizure burden–number of sites of onset and duration ○ If seizure burden greater than 40 per hour there is nine times more chance of abnormal neurodevelopmental outcome and eight times more chance if greater than 13 per hour • Status epilepticus • Neurological examination • Number of ASM required to treat • Neuroimaging findings • Gestational age baby • Small for gestational age (SGA) baby

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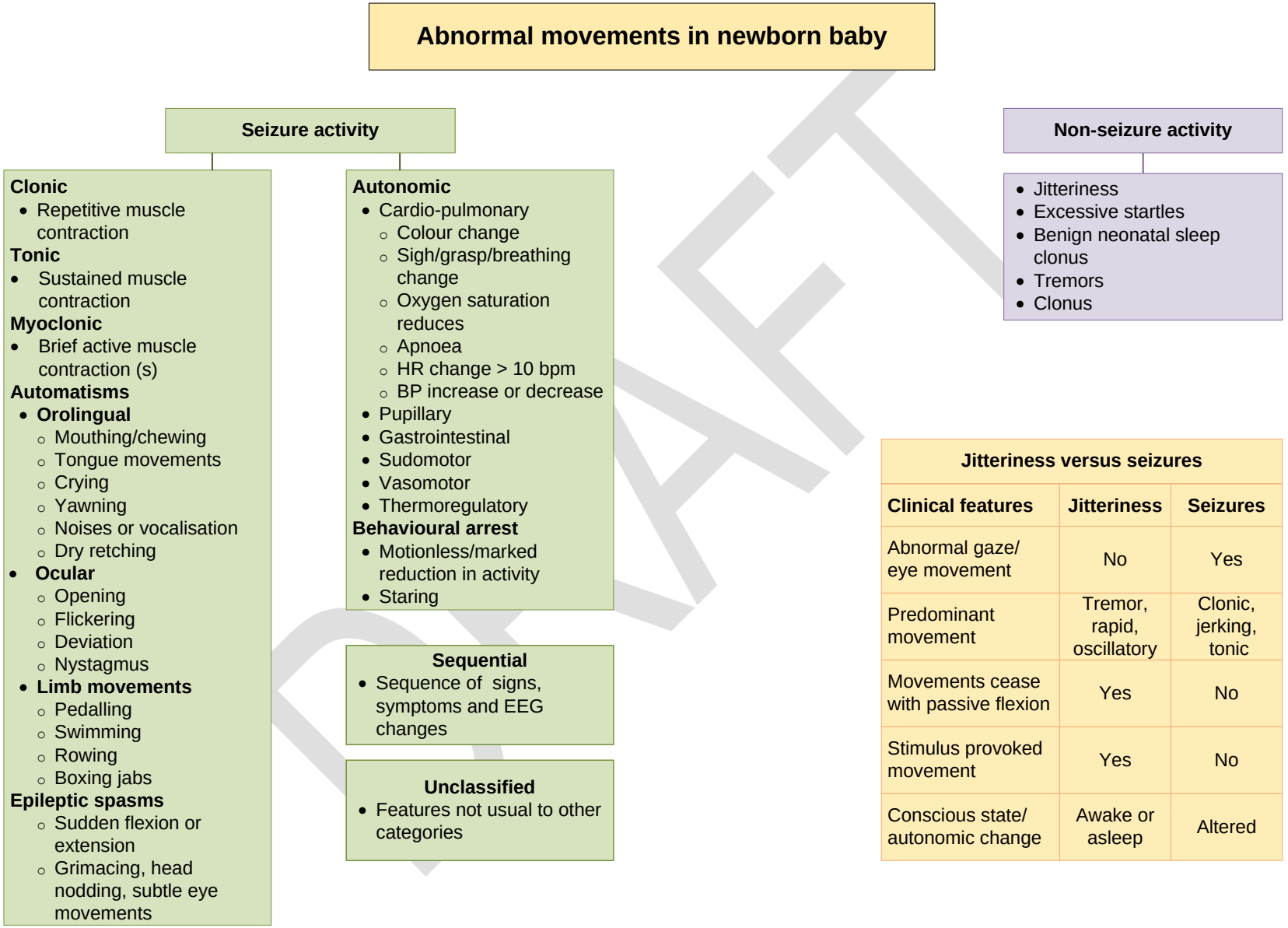
Appendix A Abnormal movements



Jitteriness versus seizures

Clinical features	Jitteriness	Seizures
Abnormal gaze/ eye movement	No	Yes
Predominant movement	Tremor, rapid, oscillatory	Clonic, jerking, tonic
Movements cease with passive flexion	Yes	No
Stimulus provoked movement	Yes	No
Conscious state/ autonomic change	Awake or asleep	Altered

Appendix B Abnormal neurological examination of term/near term baby

Aspect/test	Consideration	Abnormal
History	• Family, maternal, antenatal, intrapartum and birth • Gestational age • Apgar score and resuscitation	• Genetic family history • Birth defects • Seizures, developmental delay, thromboembolic or coagulation disorders • Stillbirths or early unexpected deaths • Difficult birth
General	• Resting posture moderate flexion of four limbs, held off bed	• Constant tight flexion • Full extension, flaccid or forced
	• Observations (temperature, heart rate, respirations, oxygen saturation, colour)	• Apnoea
	• General appearance–normal features, facial symmetry, eye movement symmetry	• Dysmorphic features, facial asymmetry, eye movement asymmetry, facial palsy
	• Examination of the skin (presence of lesions), and spine	• Hair tufts, tracts along spine • Pale pink macular lesion (portwine stain)
Head shape, size and facial features	• Fontanelles, sutures • Facial features	• Caput succedaneum • Cephalhaematoma • Subgaleal haemorrhage • Bulging fontanelles • Widely split, open sutures • Abnormal head shape with rigid sutures • Facial dysmorphism • Facial palsy • Abnormal eye movements • Sunset sign
	• Occipito-frontal circumference (10th–90th percentile)	• Microcephaly • Macrocephaly
Level of alertness	• Normal response to arousal	• Slight to moderate stupor, deep stupor or coma, irritable, lethargic
Behavioural state (state of consciousness)	• Light sleep, drowsiness, quiet alert, active alert, crying	• Stupor, coma • Irritable • Lethargic
Cry	• Loud, strong	• High pitched • Weak or monotonous
Muscle tone	• Normal	• Hypotonic • Hypertonic

Aspect/test	Consideration	Abnormal

Reflexes–Moro, suck, grasp	• Present	• Absent or asymmetric
		• Moro:
		  ○ No response or opening of hands only
		  ○ No abduction or adduction; only forward extension of arms from the shoulders; marked adduction only

Movements	• Tremor	• Continuous
	• Spontaneous limb movements	• Only stretches • Cramped synchronised (rigid and lack normal smooth and fluent character) • Mouthing • Jerky or other abnormal movements • Fisted hand(s)
Posture	• Position of limbs at rest	• Arms and legs extended or very slightly flexed • Abnormal posture–opistotonus; arm flexed, leg extended
Arm traction	• Normal resistance • Arm recoil	• Arms remain straight, no resistance • Flexion of arms < 100° maintained when body lifts up
Leg traction	• Normal resistance • Leg recoil	• Leg straight, no resistance • Knee flexion remains when back and buttocks raised

Head control	• Raises head
	• Head:
	  ○ Drops forward or back (36–37 weeks gestational age)
	  ○ May wobble (after 37 weeks gestational age)
		• No attempt to raise head from flexion
		• No attempt to raise head from extension–head remains upright or neck extended; cannot be passively flexed

Head lag	• Resistance to gravity	• Head drops and stays extended • Head in front of line of body
Ventral suspension	• Back slightly curved, limbs flexed (36–37 weeks gestational age) • Back straight, limbs flexed (after 37 weeks gestational age)	• Back curved, heads and limbs hang straight • Back straight, head above line of body

Adapted from: Hawes J, Bernardo S, Wilson D. The neonatal neurological examination: improving understanding and performance. Neonatal Network 2020;39:116-28; Kaur S, Pappas K. Genetic etiologies of neonatal seizures. Neoreviews 2020;21(10):e663-e72; Kotagal S. Neurological examination of the newborn. [Internet]. 2020 [cited 2022 June 3]. Available from: https://www.uptodate.com; Mercuri E, Ricci D, Pane M, Baranello G. The neurological examination of the newborn baby. Early Human Development 2005;81(12):947-56;

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