Queensland Clinical Guidelines

Translating evidence into best clinical practice

Maternity and Neonatal **Clinical Guideline**

Neonatal seizures

Queensland Government

Document title:	Neonatal seizures
Publication date:	May 2017
Document number:	MN17.23-V2-R22
Document supplement:	The document supplement is integral to and should be read in conjunction with this guideline.
Amendments:	Full version history is supplied in the document supplement.
Amendment date:	Full review of original document published in 2011.
Replaces document:	MN23-V1-R16
Author:	Queensland Clinical Guidelines
Audience:	Health professionals in Queensland public and private maternity and neonatal services.
Review date:	2022
Endorsed by:	Queensland Clinical Guidelines Steering Committee
	Statewide Maternity and Neonatal Clinical Network (Queensland)
Contact:	Email: Guidelines@health.qld.gov.au
	URL: www.health.qld.gov.au/qcg

Disclaimer

This guideline is intended as a guide and provided for information purposes only. The information has been prepared using a multidisciplinary approach with reference to the best information and evidence available at the time of preparation. No assurance is given that the information is entirely complete, current, or accurate in every respect.

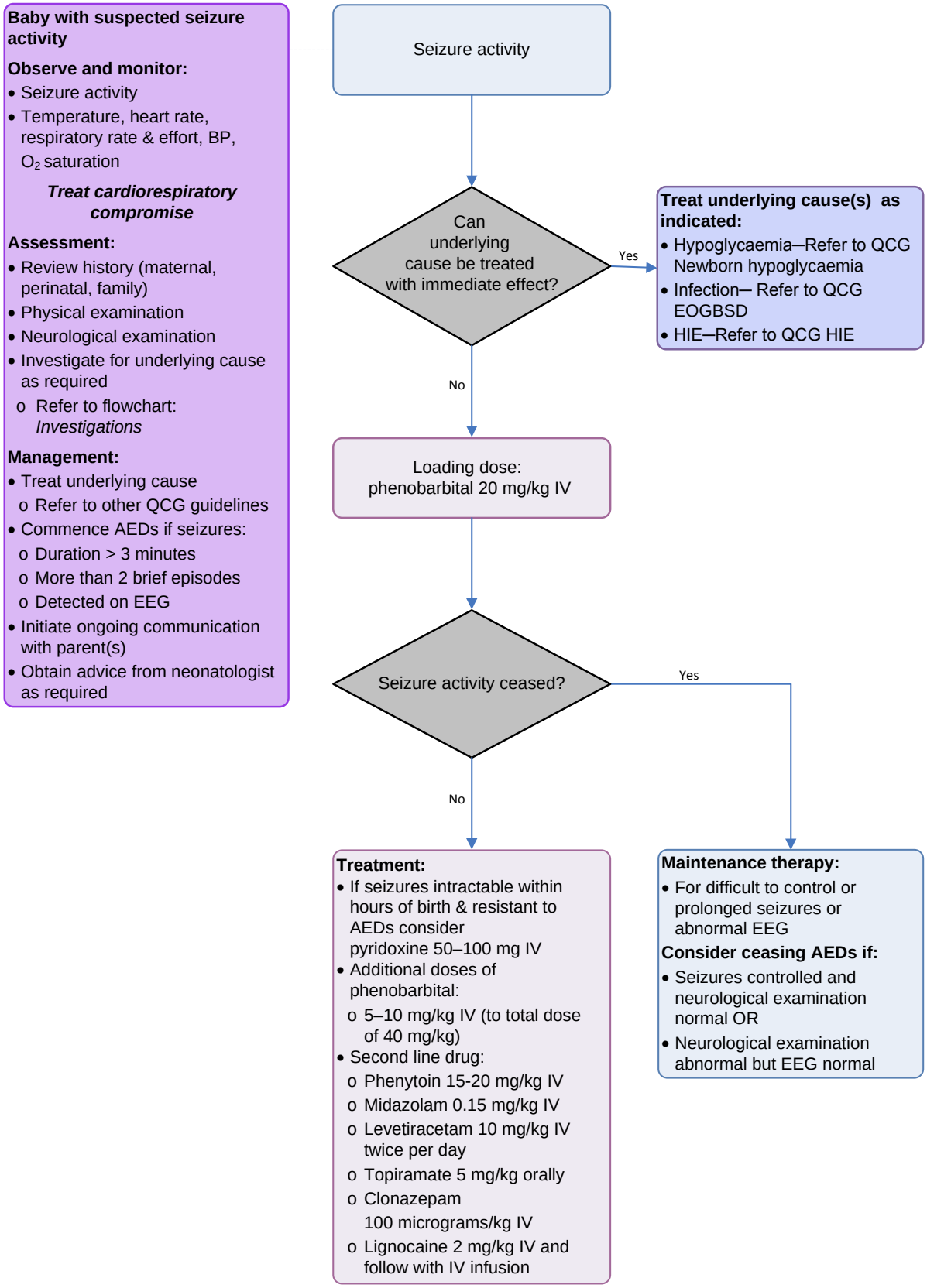
The guideline is not a substitute for clinical judgement, knowledge and expertise, or medical advice. Variation from the guideline, taking into account individual circumstances, may be appropriate.

This guideline does not address all elements of standard practice and accepts that individual clinicians are responsible for:

- Providing care within the context of locally available resources, expertise, and scope of practice
- Supporting consumer rights and informed decision making in partnership with healthcare practitioners, including the right to decline intervention or ongoing management
- Advising consumers of their choices in an environment that is culturally appropriate and which enables comfortable and confidential discussion. This includes the use of interpreter services where necessary
- Ensuring informed consent is obtained prior to delivering care
- Meeting all legislative requirements and professional standards
- Applying standard precautions, and additional precautions as necessary, when delivering care
- Documenting all care in accordance with mandatory and local requirements

Queensland Health disclaims, to the maximum extent permitted by law, all responsibility and all liability (including without limitation, liability in negligence) for all expenses, losses, damages and costs incurred for any reason associated with the use of this guideline, including the materials within or referred to throughout this document being in any way inaccurate, out of context, incomplete or unavailable.

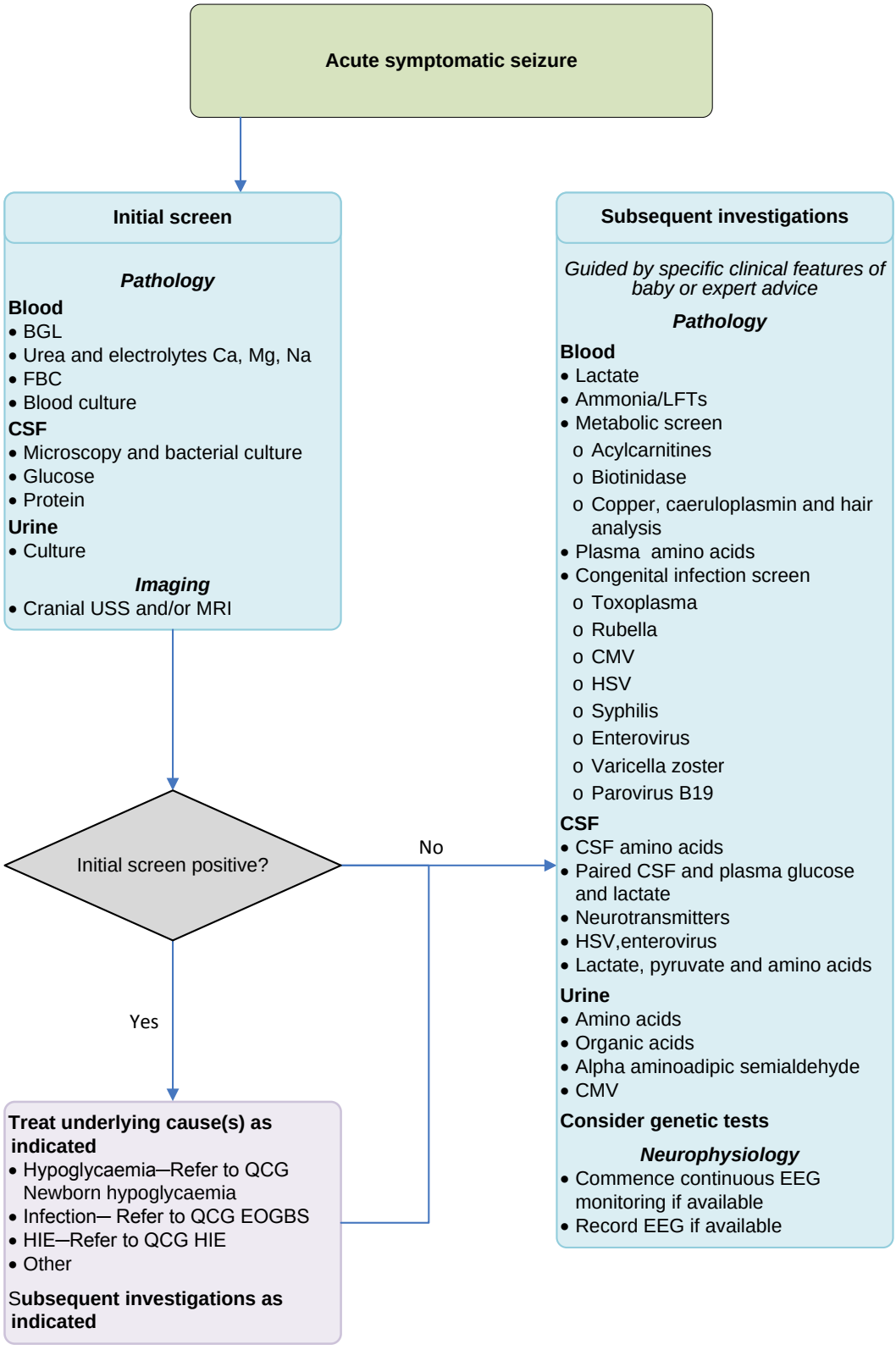
Flow Chart: Assessment and management



Abbreviations: AED: Anti-epileptic drug(s); **BP:** Blood pressure; **EEG:** Electroencephalogram; **EOGBSD:** Early onset Group B Streptococcal disease; **HIE:** Hypoxic ischaemic encephalopathy; **IV:** Intravenous; **QCG:** Queensland Clinical Guidelines, **>:** Greater than

Queensland Clinical Guidelines Neonatal seizures: F17.23-1-V1-R22

Flow Chart: Investigations



Abbreviations: 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; **LFTs** Liver function tests; **MRI** Magnetic resonance imaging; **QCG** Queensland Clinical Guidelines; **USS** Ultrasound scan

Abbreviations

AED	Antiepileptic drugs
aEEG	Amplitude integrated electro-encephalogram
BGL	Blood glucose level
BP	Blood pressure
cEEG	Continuous electro-encephalogram
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebro-spinal fluid
EEG	Electroencephalogram
GMA	General movements assessment
HIE	Hypoxic-ischaemic encephalopathy
HSV	Herpes simplex virus
IM	Intramuscular
IV	Intravenous
IVH	Intraventricular haemorrhage
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
USS	Ultrasound scan
VLBW	Very low birth weight

Definitions

Apoptosis	Cell death[1]
Automatisms	Non-purposeful, stereotyped, and repetitive behaviours most common are oral lip smacking, chewing, swallowing and cycling[2,3]; performed without conscious control[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[4]
Hyperekplexia	Neurologic disorder where there is a pronounced startle response to tactile or acoustic stimuli, and hypertonia[5]
Hypsarrhythmia	Abnormal inter-ictal pattern with electroencephalogram (EEG) high amplitude and irregular waves and spikes with background of chaotic and disorganised activity[1]
Ictal	Relating to seizures[1]
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)[1]
Opisthotonos	Abnormal extensor posture where the head and lower limbs are bent backwards and the body is arched forward[1]
Polymicrogyria	Abnormal development of the brain before birth characterised by too many folds (gyri) that are unusually small[5]
Schizencephaly	A rare congenital anomaly where unilateral or bilateral clefts in the cerebral hemispheres develop that may be filled with cerebrospinal fluid[5]
Spasticity	Muscular hypertonicity with increased resistance to stretch[5]

Table of Contents

List of Tables

1 Introduction

Neonatal seizures are a neurological emergency[6] that are difficult to diagnose and treat.[7,8] The clinical presentation of neonatal seizures is variable and clinical features of a seizure are often absent or non-specific.[6,7] This has led to under-diagnosis and occasional over-diagnosis [7] of neonatal seizures. Newborn babies can have movements that can be mistaken for seizures, where the electroencephalogram (EEG) is normal.[7]

The majority of seizures demonstrated on video EEG monitoring do not have overt clinical signs.[6] Neonatal seizures encompass events that have a proven underlying epileptic mechanism detected by an EEG.[6] They most commonly occur due to neonatal encephalopathy often due to brain hypoxic ischemia.[9] Subclinical seizures may manifest as apnoea in the term baby however when it is the sole sign of a seizure it is not usually accompanied by bradycardia.[10,11]

Seizure are a sign of neurological dysfunction and neonates[12] are at especially high risk of seizures compared to other age groups.[13] They reflect different pre-, peri-, or postnatal disorders of the central nervous system (CNS).[9] The reasons are multifactorial and include the relative excitability of the developing neonatal brain as well as the high risk for brain injury due to hypoxia, ischaemia, stroke, intracranial haemorrhage and metabolic disturbance.[13]

Seizures can be associated with greater risk of long term neurodevelopmental disablities.[8] Both clinical and electrographic seizures are associated with neurological sequalae including motor and cognitive deficits, an increased risk of epilepsy in later life and hypoxic induced brain injury as seen in hypoxic-ischaemic encephalopathy (HIE).[13]

1.1 Incidence

Seizures occur more frequently in the neonatal period than at any other time.[14,15] Preterm babies, especially those at lower gestational age and birth weights, have a higher incidence of neonatal seizures due to the associated morbidity of cerebral insults such as intraventricular haemorrhage and periventricular leucomalacia.[16,17]

Generally:

- Term babies: 1.5–5/1000 live births[8,10,18,19]
- 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: 37%–57%[15]

1.2 Consultation and referral

Clinical management is provided within the capability of the service to ensure the baby's clinical and safety needs are met.[21]

Table 1. Consultation, retrieval or transfer

Aspect	Consideration
Level 1–5	• Provide care according to Clinical Service Capability Framework[21]
Level 1	• Provide basic life support for baby • Contact local retrieval services for: o Advice and to discuss initial management with neonatologist o Retrieval to higher level service
Level 2 or 3	• Contact local retrieval services for: o Advice and to discuss initial management with neonatologist • Arrange transfer or retrieval (dependent on baby's condition) including: o BGL less than 1.5 mmol/L o Known neonatal abstinence syndrome (NAS) o Requires cardio-respiratory support o Abnormal physical or neurological examination o Seizures intractable within hours of birth and resistant to first line anti-epileptic drugs (AEDs) o Further investigations required including pathology, neuroimaging or neurophysiology • Correct abnormal blood glucose level (BGL) • Assess, manage and monitor airway, breathing and circulation • Initiate and document discussion with parents
Level 4	• Contact local retrieval services: o For advice and to discuss management with neonatologist: o If ongoing investigations not available at facility including magnetic resonance imaging and EEG o If birthweight is less than 1500 g or gestation less than 32 weeks
Level 5	• Contact local retrieval services for baby if birthweight is less than 1000 g or gestation less than 29 weeks
Retrieval or transfer	• Contact local retrieval services for retrieval or transfer to higher level service

2 Aetiology

Seizures occur when excessive and synchronised depolarisation occurs in a large group of neurons.[22] Most neonatal seizures occur in the context of a diagnosable underlying condition.[7] These conditions include poor cerebral perfusion[23] (including HIE), haemorrhage, hypoglycaemia, head trauma, electrolyte imbalance or stroke (meningitis or encephalitis).[7]

2.1 CNS causes

Table 2. CNS causes

Cause	Comment
Hypoxic-ischaemic encephalopathy	• Seen in preterm and term babies though clinical features may differ with gestation[22] • Usually present within first 72 hours of life, typically between four and 24 hours after birth[10] • May be subtle, clonic or myoclonic seizures • Results from excessive depolarisation caused by a disruption to the adenosine triphosphate (ATP)-dependent pump • Refer to Queensland Clinical Guideline *Hypoxic-ischaemic encephalopathy*[24]
Intracranial haemorrhage	• Generally more common in preterm than term babies[22] • Subdural haemorrhage[13] usually associated with cerebral contusion and more common in term babies[22] • Intraventricular haemorrhage (more common in preterm babies)[13] • Parenchymal haemorrhage[13] • Subarachnoid haemorrhage (more common in term babies)[22] • Subgaleal haemorrhage[23] • Germinal matrix intraventricular haemorrhage (IVH) (more common in preterm babies especially born before 34 weeks gestation)—subtle seizures often present[22]
Infection of CNS	• Acute infection[13] requires urgent investigation and consideration of treatment pending results • Important causes requiring urgent investigation: o Bacterial meningitis(consider *Escherichia coli* and *Steptoccocus agalactiae* (Group B Streptoccocus) and Listeria monocytogenes)[25,26] ▪ Septicaemia without meningitis may also result in seizures[10] o Encephalitis—causes include: ▪ Viruses including Herpes simplex (HSV), Enterovirus, or Cytomegalovirus (CMV)[27] ▪ Parasites such as *Toxoplasma gondii* or ▪ Bacterial pathogens such as *Escherichia coli* and *Streptococcus pneumoniae*[22] • Congenital infections[8] may also require urgent investigation and treatment if suspected active infection o Consider HSV[27], CMV, Toxoplasmosis, Syphilis (*Treponema pallidum*), Varicella zoster, Parovirus B19, Rubella[8,28,29]
Other cerebrovascular	• Arterial stroke • Venous stroke[8,13]

2.2 Other causes

Table 3. Other causes

Cause	Comment
Biochemical	• Hypoglycaemia • Hypocalcaemia • Hypomagnesaemia[8,13,22] • Hyponatraemia[8,13] • Hypernatraemia[8] • Urea cycle disturbances resulting in ammonia accumulation[10]
Inborn errors of metabolism	• Multifocal and generalised myoclonic jerks often intermixed with tonic signs, abnormal eye movement, grimacing or irritability • Time of onset: o Depends on the disorder: ▪ Disorder resulting in key metabolite deficiency can present very early (e.g. pyridoxine dependent seizures) ▪ Disorders resulting accumulation of a toxic product may present late o May also vary with severity and timing (e.g. hypoxia, infection) • Usually seen after baby starts feeding[22] • Rare inborn errors of metabolism including pyridoxine responsive seizures[8,10,30] and other vitamin dependency • Baby may be in poor condition at birth • Seizure activity may be accompanied by: o Metabolic acidosis, electrolyte disturbance, abdominal distension, feed intolerance o Misdiagnosis if HIE or sepsis are incorrectly diagnosed[30] • May have maternal report of abnormal intrauterine movements (fluttering or hiccoughs)[30,31]
Other	• Drug withdrawal syndromes[8,10] o Refer to Queensland Clinical Guidelines *Perinatal substance use—neonatal*[32] and *Perinatal substance use—maternal*[33] • Benign familial neonatal seizures o Result from gene mutation o Remit within first few months and are associated with good neurological outcomes[8] • Benign neonatal seizure syndromes o Typically present on day five o Often multifocal o CSF usually unremarkable[8,22] • A range of genetic disorders causing epilepsy syndromes e.g. early onset epileptic encephalopathy; Ohtahara syndrome
Developmental/ congenital	• Abnormality of brain development[8]

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.[6] The typical time of presentation is identified in Table 4. Presentation, but the day of onset may be variable.

Table 4. Presentation

Typical onset	Cause
Day 1[11,34]	• Traumatic brain injury: o Haemorrhage—subarachnoid, intraventricular, intracerebral o Subdural haematoma o Sub-galeal • Hypoxic ischaemic insult • Stroke (arterial) • Infection: o Viral or bacterial • Hypoglycaemia o Preterm baby o Small for gestational age o Maternal gestational diabetes o Polycythaemia • Severe neurometabolic disorders: o Sulphite oxidase deficiency o Non-ketotic hyperglycinaemia o Urea cycle defects • Drug withdrawal syndromes • Pyridoxine dependent
Day 2[11,34]	• Stroke (venous thrombosis) • Glucose transporter deficiency • Electrolyte deficiency/disturbance: o Hyponatremia o Hypernatremia o Hypocalcaemia o Hypomagnesaemia • Infection
Day 3[11,34]	• Neurometabolic disorders • Cerebral malformations: o Lissencephaly o Polymicrogyria o Schizencephaly • Other genetic abnormalities • Infection

3 Seizure description

Clinically a seizure is a paroxysmal alteration in neurological function of behavioural, motor or neurological function.[11] Underlying the clinical manifestation is an electrographic seizure.

3.1 Classification

Neonatal seizures are either clinical or electrographical (if an EEG is in place and shows a seizure pattern). Clinical seizures can be classified as:[2,35]

- Clonic–recurrent muscle contraction
- Tonic–sustained muscle contraction
- Myoclonic–brief active muscle contraction
- Subtle–automatisms, autonomic phenomena, ocular phenomena and include seizures with apnoea
- Focal–involving one part of the brain and affecting one side of the body[11]
    - Multifocal–involving more than one part of the brain affecting several body parts, asynchronous and migratory[11]
- Generalised–involving bilateral brain structures, synchronous and non-migratory[11]

3.2 Clinical presentation

Table 5. Seizure type

Aspect	Comment
Clonic[3,10,22,36]	• Rhythmic movements–usually slow at a rate of one to three per second • May involve face arms, legs or trunk • May be focal (one part or side of body) or multifocal (multiple areas of the body shifting from one site to the other) • Can be identified by clinical observation • Focal clonic have best outcomes[36] • Primarily found in term babies[37]
Tonic	• Generalised tonic seizures–sustained symmetric posturing of limbs, trunk, and neck o More common in preterm babies[20,35]who have poorer prognosis[20] o May be flexor, extensor, or mixed extensor/flexor[3] o Involve both upper and lower extremities: ▪ Tonic extension (resemble decerebrate posturing) or ▪ Tonic flexion of arms and extension of legs (mimics decorticate posturing)[10,36] ▪ May involve one extremity or whole body axial musculature in a opisthotonic fashion[22] o May be provoked or intensified by stimulation o May be suppressed by restraint or repositioning o Presumed pathophysiology is non-epileptic[3] • Focal tonic seizures of one extremity: o Especially associated with eye deviation[7] o Cannot be provoked by stimulation or suppressed by restraint[3]
Myoclonic	• Repeated often non-rhythmical, brief shock like jerks[7] • Random, single, rapid contractions of muscle groups of the limbs, face, or trunk o Tendency to affect flexor muscle groups o Caused by sudden contraction or relaxation of one or more muscles[7] • Resemble clonic movements but are quicker and gives appearance of jerky baby o Do not have rhythmical nature of clonic seizures[7] o May occur in one extremity (i.e. focal) or in several body part (i.e. multifocal) or fragmentary[3,22,36] o Typically not associated with electrographic correlates[22,36] • Typically not repetitive or may recur at a slow rate • Each one lasts approximately one microsecond or less[7] • May be provoked by stimulation[3] • Generalised myoclonic seizure more likely to have EEG changes[7] o Include burst suppression, focal sharp waves and hypsarrhythmia[36] • Occur rarely but carry worst prognosis[35,36]
Subtle	• More common in term babies[36] but also found with preterm babies[35] • May have[10,36]: o Ocular–tonic horizontal eye deviation or sustained eye opening with ocular fixation or cycle fluttering o Oral-facial-lingual movements–chewing movements, tongue thrusting, lip smacking o Limb movements–cycling, paddling, boxing jabs o Autonomic CNS phenomena–tachycardia, bradycardia o Apnoeic spells: ▪ Area rare manifestation of seizures and usually without accompanying bradycardia (unless prolonged hypoxaemia) ▪ More commonly seen in term babies than preterm[11]

3.3 Non seizure activity in babies

Table 6. Non-seizure activity

Aspect	Comment
Jitteriness	• Recurrent tremor • Reducible by tactile stimuli, holding or flexing the affected body part • Does not affect the face • Not associated with eye deviation or autonomic change[7] • Tremulousness of all limbs or just one limb • May also have a pathological basis • Commonly seen in many of the same conditions that are associated with neonatal seizures, e.g. drug withdrawal (from maternal drug ingestion), HIE, hypocalcaemia, and hypoglycaemia • Can clinically differentiate from seizures by disappearance with physical restraint (by holding the baby) and also a lack of associated features e.g. tachycardia or apnoea[10]
Excessive startles	• Markedly excessive startles relative to the stimulation, e.g. auditory, touch[10] and tonic stiffening • Can be a sign of an encephalopathy • Can also be seen in hyperekplexia[7,10] • Can be stopped by flexion of the forehead to the chest[7]
Benign neonatal sleep myoclonus	• Benign condition in which the infant has myoclonic jerks during sleep • Involves one or more limbs–more commonly observed in arms[7,10] • Limb movements in slow wave sleep often just after falling asleep or waking up • Can be quite dramatic–whole body may shake[7] o Ceases immediately when the baby awakens • Can occur in rapid succession[7,10] • May worsen if baby is held[7]
Tremor	• Involuntary generalised movement • Rhythmical oscillating around a fixed axis[7]
Clonus	• Sustained and rhythmical • Upper motor neuron lesion • 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[7]

3.3.1 Jitteriness versus seizures

Table 7. Jitteriness versus seizures

Clinical feature[10,11,38]	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	Altered

4 Diagnosis

Seizures can be difficult to diagnose because abnormal movements in the newborn baby may either be seizure activity (with seizures shown on an EEG) or simply abnormal movements without electrographic seizure.[10,19] However, electrographical seizures may not be associated with abnormal movements or other clinical correlate[19] Approximately one third of neonatal seizures display clinically correlate with simultaneous video EEG recordings.[39] The differential diagnosis for neonatal seizures is broad and includes structural, metabolic and genetic causes.[13]

4.1 Assessment of baby

Table 8. Assessment

Aspect	Comment
Clinical evaluation	• Less accurate than EEG • Does not identify subclinical or non-convulsive seizures[13]
History[10,13]	• Maternal antenatal history including: o Previous miscarriages o Gestational diabetes (causing neonatal hypoglycaemia) o Infections and any treatment received (including sexually transmitted disease) particularly HSV, Syphilis, CMV and Toxoplasmosis o Travel history for risk of Zika virus[29] that may cause congenital abnormalities including microcephaly[28] o Use of prescription and illicit drugs 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[30] • Family history of epilepsy especially maternal in infancy or other family members (consanguinity) • Perinatal history including type of birth and resuscitation and any: o Fetal distress o Birth trauma o Perinatal asphyxia
Examination[10,13]	• Physical examination: o Congenital anomalies o Head circumference as microcephaly may be indicative of underlying brain malformation o Birthmarks o Somatic abnormalities o Facial dysmorphology • Abnormal neurological examination • Signs of sepsis[refer to Queensland Clinical Guideline *Early onset Group B streptococcal disease*][40]
Observations	• Monitor and record vital signs including heart rate, respiratory rate and effort, oxygen saturations, temperature, colour, blood pressure as indicated (e.g. if phenytoin administered) • Observe and record seizure activity: o Date, time and duration of any event o Whether seizures are stereotypical with clear onset and offset o Type of seizure (subtle, tonic, clonic, myoclonic and if focal or generalised) 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

4.2 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. Investigations are stratified according to possible cause and initial investigations are undertaken when a baby presents with neonatal seizures.

Table 9. Initial investigations

Aspect	Comment/good practice point
Blood[10,30]	• BGL • Urea, electrolytes and calcium, magnesium and sodium • Full blood count • Blood cultures
CSF[13,41]	• Microscopy and bacterial culture • PCR (bacterial and viral) • Glucose • Protein • Blood • Colour
Urine[10]	• Microscopy and culture
Imaging[13,36]	• USS for detection of intra-ventricular and parenchymal haemorrhage[36] • Magnetic resonance imaging: o Preferable to computed tomography or (USS) o Greater sensitivity in identifying brain malformations, intracranial haemorrhage and ischaemic damage[10] o Does not aid the diagnosis of seizures but can be useful for diagnosing intracranial lesions associated with seizures[42] o Use if the aetiology is not identified and seizures resistant to usual AEDs o Diagnostic for cerebral dysgenesis, lissencephaly and other neuronal migration disorders[36] 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 4–8 for baby with HIE [Refer to Queensland Clinical Guideline *Hypoxic-ischaemic encephalopathy (HIE)]*[24]

4.3 Subsequent investigations

Table 10. Subsequent investigations are guided by the baby's clinical features or expert opinion.

Table 10. Subsequent investigations

Aspect	Comment
Blood[10,30,43]	• Lactate • Ammonia • Liver function tests • Thrombophilia screen • Metabolic screen o Acylcarnitines[41] o Biotinidase o Copper, caeruloplasmin and hair analysis o Amino acids
CSF[10,11,43,44]	• Amino acids • Neurotransmitters • HSV, Enterovirus • Lactate, pyruvate and amino acids • Paired CSF and plasma glucose, lactate and pyruvate[11,30]
Urine[10,36]	• Organic acids[3] • Metabolic screen including ketones, reducing substances, amino acids • Alpha aminoadipic semialdehyde • CMV[35]
Other	• Congenital infection screen[10,35,43] o Toxoplasmosis o Rubella o CMV o HSV o Syphilis o Enterovirus o Varicella zoster o Parovirus B19 • Consider genetic tests[3,13,43]
Neurophysiology	• Commence continuous EEG monitoring if available[13] • Record EEG if available[6] • EEG: o Has a diagnostic and prognostic role o Only way to confirm clinical event is seizure activity[6,13,42] ▪ A standard non-continuous EEG of 30 minutes may be performed when there is no seizure activity and result in a false negative result • Conventional, prolonged, continuous video-EEG (cEEG): o Gold standard for detecting neonatal seizures[6,13,42] o Recommended for babies at high risk for seizures and/or paroxysmal events[13] • Amplitude integrated EEG (aEEG): o Convenient bedside tool with only four electrodes o Lower sensitivity and specificity than cEEG o Lower sensitivity for brief, focal seizures or distant from recording electrodes[13] Useful also for monitoring background brain activity (e.g. identifying variability as a sign of neurological wellbeing) • Identification of longer duration seizures and status epilepticus[6]

5 Management and treatment

The principles for acute symptomatic neonatal seizure management include:[8,13,35]

- Rapid and accurate identification of seizures clinically and where possible by EEG
  - EEG is usually not available during first clinical seizure
- Avoidance of misdiagnosis
- Titration of medication(s) to stop electrographic seizures
- Early discontinuation of medications once seizures have ceased
- Prevention of secondary problems by maintaining normal physiological temperature, blood glucose, oxygenation, ventilation and blood pressure

5.1 Observation and monitoring

Table 11. Initial assessment and management

Aspect	Comment/good practice point
Resuscitation	• Establish adequate airway, ventilation and perfusion[13,35,39] o Minimise additional postnatal hypoxaemia and hyper- or hypocapnia • Commence cardio-respiratory, oxygen saturation and blood pressure monitoring in babies: o At risk of encephalopathy including alterations in autonomic functioning (vital signs) which may be indicative of seizure activity o Being administered anticonvulsant medication • Obtain intravenous (IV) access
Assessment/ examination	• Undertake comprehensive history and assessment of baby: o Refer to Table 8. Assessment o Refer to Table 9. Initial investigations • Commence early discussions with neonatologist for paediatric neurology input through local retrieval services regarding assessment, initial management and potential for transfer to tertiary neonatal unit
Treat underlying causes	• Biochemical causes e.g. hypoglycaemia[13,35] [refer to Queensland Clinical Guideline *Newborn hypoglycaemia*[45]] • Suspected bacterial infection according to local protocols or with empirical antibiotic therapy [refer to Queensland Clinical Guideline *Early onset Group B Streptococcal disease* for dosing regimens[40]] o Commence: ▪ Benzyl penicillin IV **AND** gentamicin IV **OR** ▪ Amoxicillin/ampicillin IV **AND** gentamicin IV **AND** o Also commence Cefotaxime IV if bacterial meningitis is suspected • Commence Acyclovir IV until CSF PCR for HSV is known to be negative • Other underlying causes[35] e.g. HIE–refer to Queensland Clinical Guideline *Hypoxic-ischaemic encephalopathy*[24] • In the absence of hypoglycaemia commence AED[35] • Treat other common biochemical derangements such as: o Hypocalcaemia[8]–with 10% calcium gluconate IV 2 mL/kg over 10 minutes and with cardiac monitoring[36,46] o Hypomagnesaemia[8]–with 50% magnesium sulphate[36] deep intramuscular injection 100 mg/kg[46] • If maternal substance use known or suspected—consider neonatal abstinence syndrome—refer to Queensland Clinical Guideline *Perinatal substance use–neonatal* and Queensland Clinical Guideline *Perinatal substance use–maternal*[32,33]

5.1.1 Continuing care

Table 12. Continuing care

Aspect	Comment/good practice point
Medications	• Refer to Section 6 Drug therapy
EEG	• Commence EEG monitoring if available, ideally with video recording • Clinical observation alone may: o Over detect apparent seizure activity that has no EEG correlate[39] o Under detect clinical seizures that are identified on EEG[39] • Majority of electrographic seizures do not have any overt clinical signs[19]
Model of care	• Provide family centred care • Establish early and ongoing communication with parents o 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 o 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
Referral	• Consider: o Early discussion with neonatologist regarding assessment, diagnosis and potential for transfer to higher level nursery o Telehealth • Refer to Queensland Clinical Guideline *Neonatal stabilisation for retrieval*[47]
Documentation	• Document any episode of unusual or stereotypical movement and alterations in autonomic functioning Refer to Table 8. Assessment • Video (if available) abnormal movements simultaneously with recording of cardiorespiratory monitoring

6 Drug therapy

While pharmacological options for treatment of neonatal seizures have increased there is limited evidence regarding the optimal pharmacological treatment strategy. Consider benefits and risks of available options including potential efficacy, potential toxicity and side effects and anticipated rapidity of response.[48] Phenobarbital is recommended as the drug to be used but there is no general agreement on the preferred drug(s) for second line treatment.

Table 13. 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 AEDs used to treat neonatal seizures[13,49] • Experimental data shows commonly used AEDs may cause neurotoxicity and neuronal apoptosis[13,50,51] • Anticonvulsant drugs may not stop electroencephalographic seizures even if they are effective in reducing or eliminating the clinical manifestations (electro-clinical dissociation)[42] • Hypothermia and the re-warming phase of HIE management may alter AED pharmokinetics[52] o Refer to Queensland Clinical Guideline *HIE*[24]
Expert recommendations	• Administer an adequate loading dose[38] following drug administration recommendations • Treat both clinical and subclinical seizures as they have similar pathophysiology • Phenobarbital is the preferred first line medication[13,53] o Refer to Table 14. 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[51] • Commence treatment when: o Clinically apparent seizure lasts more than three minutes o More than two briefer seizures occur o Electroencephalographic seizures are present[42] • Administer AEDs: o Intravenously to achieve rapid onset of action and predictable blood levels o To achieve serum levels in the therapeutic range o To maximum dosage before introducing another AED[38]
Maintenance and duration of treatment	• Optimal duration of treatment with anticonvulsants is unknown[13,54-56] • Consider discussion with neonatologist or paediatric neurologist before introducing second line AED • Duration of treatment considerations include: o Baby's neurological status o EEG o Underlying aetiology[57] • Cease anticonvulsants when free of seizures for 72 hours and neurological examination is normal[42,57] • Targeted maintenance treatment for genetic and metabolic disorders usually lifelong[42,57] • Treatment usually continued if there is known progress to epilepsy (e.g. structural brain malformations and neonatal epilepsy syndromes)

6.1 Anti-epileptic drugs

6.1.1 Phenobarbital

Table 14. Phenobarbital

Phenobarbital*	
Dose and administration	• First line treatment • May be diluted to 10 mg/mL in 0.9 % sodium chloride[58] • May be diluted 1:10 with water for injections[46,59] • **Loading dose:** 20 mg/kg IV[13] over 15–30 minutes[46,58] o No faster than 1 mg/kg/minute[59] • For refractory seizures administer: o Additional doses of 5–10 mg/kg IV up to a total of 40 mg/kg (including initial dose) OR o One additional dose of 20 mg/kg IV • **Very low birth weight** (VLBW; less than 1500 grams) preterm baby: o May require less than 15 mg/kg IV
	• **Maintenance:** o Commence only if seizures continue after the loading doses • 3–4 mg/kg IV per day o Commence 12–24 hours after loading dose o Daily dose (12 hourly not necessary)[46,58] • **VLBW** (less than 1500 grams) preterm baby: o Single injection of less than 3 mg/kg 24 hours later[58]
Comment	• Controls seizures in 43–85 % of babies • A second line drug is often required o Phenobarbital may be discontinued when there is a therapeutic level of the second line drug • Therapeutic range of phenobarbital is 15–40 micrograms/mL taken before fifth dose • Drug accumulation may occur during first two weeks of life • If phenytoin or valproate also administered altered levels may occur • May cause extravasation and phlebitis • Serum half-life is 40–200 hours[58] limits need to wean when short term therapy[13] • Side effects include respiratory depression, depressed level of consciousness, hypotension and hypotonia[13] • Pharmokinetics are affected by therapeutic hypothermia[46] o Refer to Queensland Clinical Guideline *Hypoxic-ischaemic encephalopathy*[24]

*Refer to an Australian pharmacopoeia for complete drug information

6.1.2 Phenytoin

Table 15. Phenytoin

Phenytoin*	
Dose and administration	• Second line anticonvulsant for seizures refractory to phenobarbital[58] • **Loading dos**e: 15–20 mg/kg IV over 30–60 minutes[46,58,59] • **Maintenance:** 5 mg/kg per day[58] or 2 mg/kg every 8–12 hours[46] • **Administration (loading and maintenance)** o Dilute to 5 mL with 0.9% sodium chloride and precede and follow injection with 0.9% sodium chloride flush to avoid contact with glucose solution[46] o Administer directly into large peripheral or central vein through large bore catheter o Do not exceed infusion rate of 1–3 mg/kg/minute[58] o Do not administer by intramuscular route as may cause soft tissue necrosis at injection site and is poorly absorbed with drug crystallisation in muscle[58]
Comment	• Monitor cardiac rhythm and rate and blood pressure and respiratory function during and after administration (for at least 15–60minutes)—May cause arrhythmias and severe hypotension[13,46,58] • Observe for extravasation and necrosis • Use with caution in babies with hyperbilirubinaemia[13] • Measure trough level 48 hours after loading dose—therapeutic level:6-15 micrograms/mL in first weeks and then 10–20 micrograms/mL • Half-life is unpredictable[46] • Dose related adverse events include nystagmus (level 15–25 mg/mL) and ataxia and mental statues changes (level greater than 30 mg/mL)[58]

*Refer to an Australian pharmacopoeia for complete drug information

6.1.3 Midazolam

Table 16. Midazolam

Midazolam*	
Dose and administration	• Second line anticonvulsant for seizures refractory to phenobarbital • **Loading dose:** 0.15 mg/kg (150 micrograms/kg) IV over five minutes • **Maintenance IV infusion:** 60–400 micrograms/kg/ hour (1–7 micrograms/minute) • **Administration (loading and maintenance)** o Dilute in 0.9% sodium chloride or 5% glucose o Do not administer by rapid infusion as may cause respiratory depression, severe hypotension and seizures[58]
Comment	• May cause myoclonic jerking[46] • May cause respiratory depression and hypotension when used in conjunction with narcotics[58] • Avoid extravasation[58] • Seldom arrests EEG evidence of seizure activity if phenobarbital has not been successful[46]

*Refer to an Australian pharmacopoeia for complete drug information

6.1.4 Levetiracetam

Table 17. Levetiracetam

Levetiracetam*	
Dose and administration	• Second line anticonvulsant for seizures refractory to phenobarbital[58] • **Loading** dose not required but may be given if urgent seizure control required[46] o No loading dose—10 mg/kg IV twice per day increasing by 10 mg/kg/day over three days to 30 mg/kg IV twice per day o If loading dose—40 mg/kg IV followed by 10 mg/kg IV once per day[46] • Dilute to a concentration 5–15 mg/mL and infuse over 15 minutes[58] • **Maintenance** dose may be given orally without regards to feeds[58] • 10 mg/kg/dose orally every daily or in two divided doses increasing by 10 mg/kg/day over three days to 30 mg/kg/day[46,58]
Comment	• Therapeutic levels monitoring generally not required but are approximately 10–40 micrograms/mL • Side effects include mild sedation, drowsiness and irritability[13] • Taper doses when discontinuing as abrupt withdrawal increases risk of seizures • Data regarding adverse effects in neonates is limited to case reports and abstracts[58] • Does not induce cell death in the developing brain (apoptosis)[46,60]

*Refer to an Australian pharmacopoeia for complete drug information

6.1.5 Topiramate

Table 18. Topiramate

Topiramate*^	
Dose and administration[46]	• May be considered as second line anticonvulsant for seizures refractory to phenobarbital • If normothermia: o **Dose:** 5 mg/kg orally once every 24 hours • If therapeutic hypothermia: o **Loading dose** 5 mg/kg orally on day 1 o **Maintenance**— 3 mg/kg orally once per day for duration of hypothermia
Comment[46]	• Broad-spectrum AED used to treat adults and children and increasingly 'off label' use for difficult to treat neonatal seizures • Does not exacerbate apoptosis after a severe hypoxic ischemic insult • May have anti-epileptogenic and neuroprotective effects[61] • The gap between effective and neurotoxic doses (50 mg/kg) is greater for topiramate than other commonly used AEDs o Short courses appear to have few neurotoxic effects[62] • Is associated with cognitive and neuropsychiatric adverse events • Pharmacokinetic and safety data for long tern use has not been established in neonatal population

*Refer to an Australian pharmacopoeia for complete drug information
^Topiramate is not on the Queensland Health (QH) List of Approved Medications (LAM)

6.1.6 Clonazepam

Table 19. Clonazepam

Clonazepam*	
Dose and administration	• Second line treatment for seizures[58] • **Dose:** 100 micrograms/kg IV over five minutes once/day for 2 to 3 days[46]
Comment	• Adverse effects include drowsiness, bronchial hypersecretion and salivation[46,58] • Seldom arrests EEG evidence of seizure activity if phenobarbital has not been successful[46] • Sedative effect may mask cortical seizure activity that has not been suppressed • Concurrent treatment with phenytoin reduces the half-life of clonazepam[46]

*Refer to an Australian pharmacopoeia for complete drug information

6.1.7 Lidocaine (lignocaine)

Table 20. Lidocaine (lignocaine)

Lidocaine (lignocaine)*	
Dose and administration	• Used for severe recurrent or prolonged seizures not responding to first line treatment • **Loading dose** for term normothermic babies: 2 mg/kg IV injection over 10 minutes followed immediately by maintenance infusion • **Maintenance** IV infusion: 6 mg/kg/hour for 6 hours; then 4 mg/kg/hour for 12 hours; then 2 mg/kg/hour for 12 hours[13,46]
Comment	• Dosing depends on gestation and the presence of hypothermia[46] • Preterm and hypothermic babies at risk of drug accumulation • Do not use: o Concurrently with phenytoin because of cardiac effects or o In babies with congenital heart disease[13] • Monitor ECG, blood pressure and heart rate • Only use preservative free ampoules without adrenaline (epinephrine)[58]

*Refer to an Australian pharmacopoeia for complete drug information

6.2 Pyridoxine (vitamin B6) deficiency

Table 21. Pyridoxine

Pyridoxine (vitamin B6)	
Diagnosis and treatment	• Classic presentation is intractable seizures that appear within hours of birth and are resistant to conventional AEDs o Baby responds rapidly to IV Pyridoxine[63] • May present with frequent multifocal and erratic or generalised myoclonic jerks o May also present with tonic seizures, spasms, abnormal eye movements, grimacing or irritability • Seizures may occur without ictal changes on the EEG[63] • Maternal history may report sensation of sustained hammering lasting 15–20 minutes by fetus inutero[63]
Dose and administration	• Used for diagnosis and treatment of pyridoxine dependent seizures • 50–100 mg IV injection[46,58] over 20 minutes[59] or IM o If required may be repeated after 10 minutes up to a total maximum dose of 500 mg[59] • If responsive then administer 50–100 mg orally[35,46,58] once per day[59]
Comment	• Vitamin B6 is a required enzyme in the biosynthesis of dopamine and serotonin • Used to treat inborn error of metabolism due to antiquitin deficiency (α-amino adipic semialdehyde [α-AASA] dehydrogenase deficiency)[30] • Consider pyridoxine dependency in any baby with severe seizures even if there is a clear cause (e.g. birth asphyxia)[46] • Seizures are usually multifocal and clonic at onset and progress rapidly to status epilepticus • Observe for bradycardia, apnoea, hypotension and hypotonia o Monitor cardio-respiratory function o Ventilator support may be necessary[8,58] • Best administered while EEG monitoring[8] but absence of EEG should not delay administration[46] • A pyridoxine level of less than 20 nanomoles/L is indicative of a deficiency[58]

*Refer to an Australian pharmacopoeia for complete drug information

7 Ongoing care

7.1 Discharge planning

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

- A seizure emergency management plan
- 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
- Copies of referrals to other services
- Follow up appointments if available

7.2 Prognosis

Neonatal seizures can cause both acute effects and long term sequelae. Acute and long term adverse effects result from energy failure, excitotoxicity, neuronal death, apoptosis and status epilepticus. These all contribute to cognitive, motor and behavioural problems.[64]

Table 22. Prognosis and outcome

Aspect	Comment
Prognosis	• Determined by aetiology[2,22] • Strongest predictors of outcome–underlying cause and background EEG activity[20,22,65] • Tends to be worse for preterm babies[11] as often associated with underlying brain injury[20,65] • If EEG background is normal: o Prognosis is excellent for resolution of seizures o Normal development is likely[22]
Morbidity and mortality	• Risk of long term morbidity and neonatal mortality[22] • Complications include[22]: o Cerebral palsy o Cerebral atrophy o Hydrocephalus ex-vacuo o Microcephaly o Epilepsy o Spasticity o Feeding difficulties

7.3 Outcomes

Babies who experience neonatal seizures are more likely to have neurodevelopmental disability and are at greater risk of developing epilepsy[20].

Table 23. Outcomes

Aspect	Comment
High risk of poor outcome	• Relatively poor long term outcomes associated with diffuse brain injury including: o Generalised myoclonic seizures o Generalised tonic seizures o Motor automatisms (subtle seizures)[2] • Other factors associated with poor outcome include o Severe abnormalities on neurologic examination[2] • Prematurity especially those with most serious life threatening illnesses o Early onset (within 48 hours of birth) o Repeated seizures of greater than or equal to one hour in duration o Recurrent seizures of greater than 48 hours[2] • Cerebral dysgenesis • CNS infection • Severe IVH • Severely abnormal EEG inter-ictal activity[65] (isoelectric pattern, paroxysmal, burst-suppression and low voltage background)[20] • More than one AED to control seizures • Less strongly associated: o Severely abnormal neurological examination o Severely abnormal neuroimaging o Early onset seizures (within 24 hours of birth related to HIE in term babies) o Severity of seizures o Presence of status epilepticus[20,65]
Associated with favourable outcome	• Normal neurological examination[20] • Focal brain injury and relatively sparing of greater regions of brain tend to have more favourable outcomes[2] • Focal clonic seizures: o Including benign familial neonatal seizures[2,20] o Benign idiopathic neonatal seizures o Transient metabolic disturbance (e.g. hypocalcaemia)[20,65] o Focal lesions (brain haemorrhage or stroke) on MRI[20] o Lesion confined to relatively circumscribed areas of the brain[2] • Brief or rarely reoccurring seizures • Clinical seizures with no EEG correlate • Normal inter-ictal EEG • Neonatal sleep myoclonus • Less strongly associated: o Normal/mild abnormality on neuroimaging o Late onset (i.e. greater than five days of age; related to benign neonatal seizures) o Focal clonic seizures (likely related to focal structural lesion in the brain)[20]

7.4 Follow up

Table 24. Follow up

Aspect	Comment/good practice point
Context	• Preterm babies are at greater risk of poor neurodevelopmental outcomes[42] • Follow up by multidisciplinary team to asses developmental outcomes[10] • 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: o General practitioner and child health nurse o Paediatrician in local area o Paediatric neurologist or neonatologist according to local arrangements if baby discharged home on AEDs ▪ Telehealth may be used where available o Multi-disciplinary team to identify any motor and cognitive deficits and timely neuro-developmental early invention[66,67] using simple tools such as the General Movements Assessment (GMA), parent screening and use of Ages and Stages questionnaire[68] ▪ Early intervention when the brain is most plastic minimises developmental disabilities[66] ▪ Abnormal fidgety GMA at three months of age is predictive for neurodevelopmental delay such as cerebral palsy[66,69] ▪ GMA requires 15 minutes of observation of the baby by a trained observer in the fidgety movements stage (i.e. three months corrected age) and has been validated in term (with HIE) and preterm babies[69] as a predictor of cerebral palsy.[67] ▪ Review by appropriately trained clinicians of GMA video recording is required. • Provide parents with a written seizure emergency management plan and a copy of the discharge plan including the types of seizures the baby had and any medication used to treat

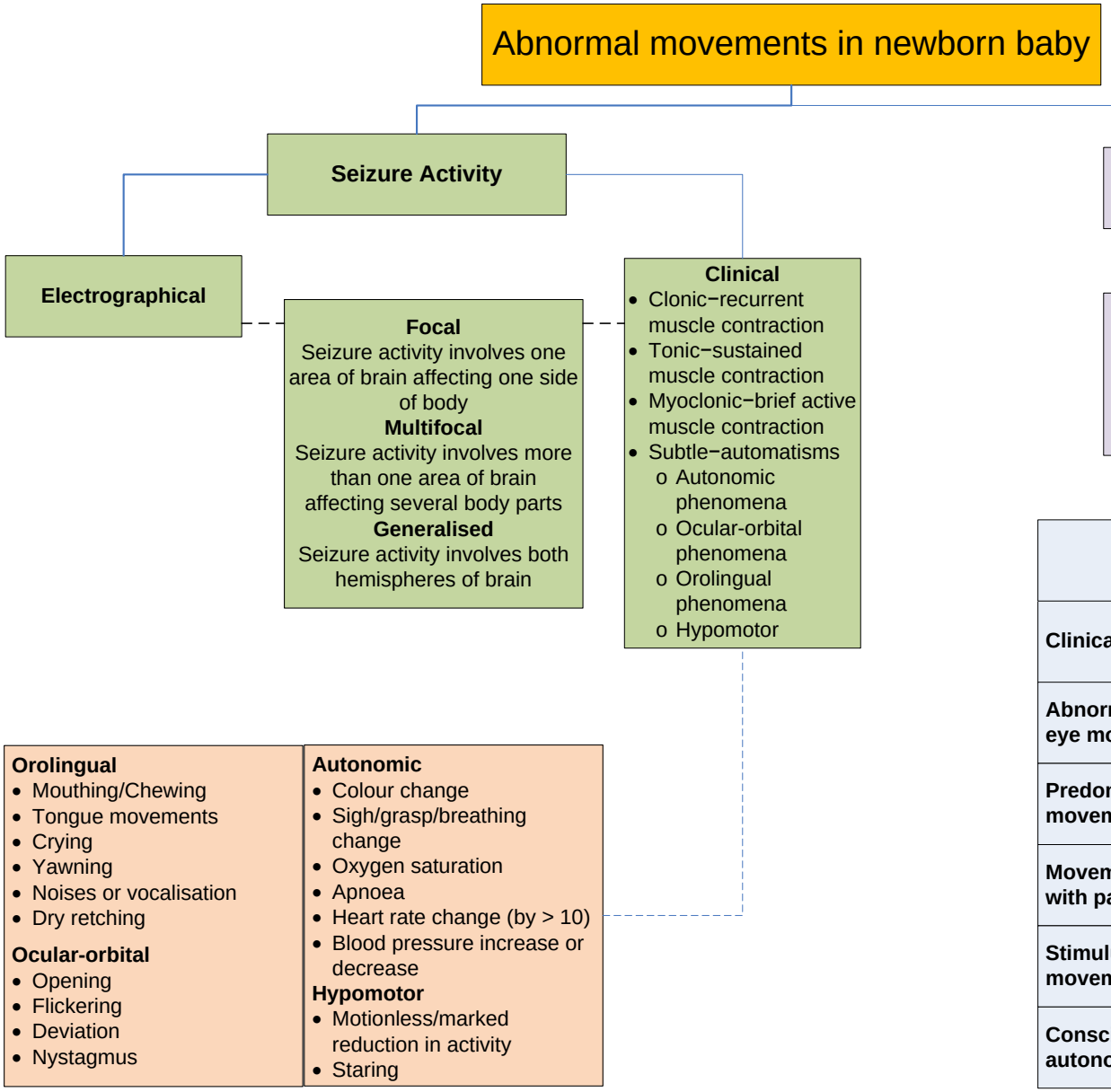
References

1. Merriam-Webster Medical Dictionary [Internet]. Apoptosis. 2017.
2. Co J, Elia M, Engel J, Guerrini R, Mizrahi E, Moshe S, et al. Proposal of an algorithm for diagnosis and treatment of neonatal seizures in developing countries. Epilepsia 2007;48(6):1158-64.
3. Scher M. Neonatal seizures. In: Avery's diseases of the newborn 9th edition. In: Avery's diseases of the newborn 9th edition: Saunders; 2012.
4. John Hopkins Medicine. Hydrocephalus. 2017 [2 February 2017]; Available from: http://www.hopkinsmedicine.org/healthlibrary/conditions/adult/nervous_system_disorders/hydrocephalus_22,neu002
5. Harris P, Nagy S, Vardaxis N. Mosby's Dictionary of Medicine, Nursing and Health Professions, Australian and New Zealand Edition, Third Australian and New Zealand Edition 2014 [cited 17 January 2017]. Available from: https://www.clinicalkey.com.au/nursing/#!/content/book/
6. Boylan G, Stevenson N, Vabhatalo S. Monitoring neonatal seizures. Seminars in Fetal & Neonatal Medicine 2013;18:202-8.
7. Hart A, Pilling E, Alix J. Neonatal seizures—part 1: Not everything that jerks, stiffens and shakes is a fit. Arch Dis Child Educ Pract Ed
2015;100:170-75.
8. Jensen F, Silverstein F. Neonatal seizures. In: Swaiman's Pediatric Neurology: Principles and Practice 5th edition [Internet]. In: Swaiman K, Ashwal S, Ferriero DM, NF S, editors. Edinburgh: Elsevier; 2012 [Cited 2016 Aug 15]. . Available from: ClinicalKey Australia.
9. Pressler R, Mangum B. Newly emerging therapies for neonatal seizures. Seminars in Fetal & Neonatal Medicine 2013;18:216-23.
10. Sivaswamy L. Approach to neonatal seizures. Clinical Pediatrics 2012;51(5):415-25.
11. Volpe J. Neonatal seizures [Internet]. Saunders; 2008 [cited 2016 Aug 22]. .
12. Verklan T, Walden M. Core Curriculum for Neonatal Intensive Care Nursing 5th edition. USA: Elsevier; 2010.
13. Glass H. Neonatal seizures: advances in mechanisms and management. Clin. Perinatol 2014;41(1):177-90.
14. Cilio M. Neonatal epilepsies and epileptic encephalopathies. In: Nagarajan, L editor. Neonatal Seizures: Current Treatment and Future Challenges. London: Mac Keith Press; 2016.
15. Rao S, Lewis B, Ghosh S, Nagarajan L. Clinical approach to neonatal seizures. In: Nagarajan L, editor. Neonatal seizures: current treatment and future challenges. London: Mac Keith Press; 2016.
16. Greisen G, Hellstrom-Wellas L, Rosen I, Svenningsen N. EEG depression and germinal layer haemorrhage in the newborn. Acta Paediatrica Scandinavica 1987;76(3):519-25.
17. Kubota T, Okumura A, Hayakawa F, Kato T, Itomi K, Kuno K, et al. Combination of neonatal electroencephalography and ultrasonography: sensitive means of early diagnosis of periventricular leukomalacia. Brain and Development 2002;24:698-702.
18. Glass H, Pham T, Danielsen B. Antenatal and intrapartum risk factors for seizures in term newborns: A Population-Based Study, California 1998-2002. J. Pediatr 2009;154(1):24-8.
19. Glass H, Shellhaas R, Wusthoff C, Chang T, Abend N, Chu C, et al. Contemporary Profile of Seizures in Neonates: A Prospective Cohort Study. J Pediatr 2016;174:98-103.
20. Uria-Avellanal C, Marlow N, Rennie J. Outcome following neonatal seizures. Seminars in Fetal & Neonatal Medicine 2013;18:224-32.
21. Department of Health. Neonatal Services V 3.2
Clinical Services Capability Framework [Internet]. 2016 [cited 21/12/2016]. Available from: https://www.health.qld.gov.au.
22. Sheth R, Hobbs J, Mullett M. Neonatal seizures: incidence, onset, and etiology by gestational age. Journal of Perinatology 1999;19(1):40-3.
23. Colditz M, Lai M, Cartwright D, Colditz P. Subgaleal haemorrhage in the newborn: A call for early diagnosis and aggressive management. Journal of Paediatrics and Child Health 2015;51:140-46.
24. Queensland Clinical Guidelines. Hypoxic ischaemic encephalopathy. Guideline No. MN16.11-V6-R21. [Internet]. Queensland Health. 2016. [cited 1 September 2016]. Available from: http://www.health.qld.gov.au
25. Edwards MS, Baker CJ. Bacterial meningitis in the neonate: treatment and outcome V14. Up to date 2016.
26. Heath PT, Nik Yusoff NK, Baker CJ. Neonatal meningitis. Archives of Disease in Childhood Fetal Neonatal Edition 2003;88:F173-F8.
27. Palasanthiran P, Starr M, Jones C, Giles M. Management of Perinatal Infections. Sydney: Australasian Society for Infectious Diseases; 2014.
28. RANZCOG. Care of women with confirmed Zika virus infection during pregnancy in Australia. 2016.
29. Russel K, Oliver S, Lewis L, Barfield W, Cragan J, Meaney-Delman D, et al. Update: Interim guidance for the evaluation and management of infants with possible congenital zika virus infection-United States, August 2016. MMWR Morb Mortal Wkly Rep 2016 2016;65:870-8.

30. Rahman S, Footitt E, Varadkar S, Clayton P. Inborn errors of metabolism causing epilepsy. Developmental Medicine & Child Neurology 2012;55:23-36.
31. Surtees R, Wolf N. Treatable neonatal epilepsy. Arch Diseases Children 2007;92:659-61.
32. Queensland Clinical Guidelines. Perinatal substance use-neonatal Guideline No. MN 16.38-V1-R21. [Internet]. Queensland Health. 2016. [cited 1 September 2016]. Available from: http://www.health.qld.gov.au
33. Queensland Clinical Guidelines. Perinatal substance use-maternal. Guideline No. MN16037-V1-R21. [Internet]. Queensland Health. 2016. [cited 1 September 2016]. Available from: http://www.health.qld.gov.au
34. Holmes G. Neonatal seizures. In Clinical Key [Internet]. 2013 May 8 [Cited 1 September 2016].
35. Roland E, Hill A. Neurological problems of the newborn. In: Daroff R, Mazziotta J, Pomeroy S, Jankovic J, editors. Bradley's Neurology in Clinical Practice. 7th ed. London: Elsevier 2016.
36. Sankar J, Agarwal R, Deorari A, Paul V. Management of Neonatal Seizures. Indian J Pediatr 2010;77:1129-35.
37. Roland E, Hill A. Neurological problems of the newborn. In: Bradley's neurology in clinical practice 7th edition [Internet] Daroff, R Jankovic, J Mazziotta, J Pomeroy, S editors. London: Elsevier; 2016 [cited 2016 Aug 22] Chapter 111. Available from CKN.
38. Levene M. Recognition and management of neonatal seizures. Paediatrics and Child health 2008;18(4):178-82.
39. Murray D, Boylan G, Ali I, Ryan C, Murphy B, Connolly S. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. Archives of Disease in Childhood - Fetal and Neonatal Edition 2008;93:F187-89.
40. Queensland Clinical Guidelines. Early onset Group B Streptoccal disease. Guideline No. MN16.20-V3-R21. [Internet]. Queensland Health. 2016. [cited 9 December 2016]. Available from: http://www.health.qld.gov.au
41. Loman A, ter Horst H, Lambrechtsen F, Lungsing R. Neonatal seizures: Aetiology by means of a standardized work-up. European Journal of Paediatric Neurology 2014;18:360-7.
42. World Health Organisation. Guidelines on neonatal seizures. Switzerland; 2011.
43. Hart AR, Pilling E, Alix J. Neonatal seizures—part 2: Aetiology of acute symptomatic seizures, treatments and the neonatal epilepsy syndromes. Arch Dis Child Educ Pract Ed 2015;100:226-32.
44. Kneen R, Solomon T, Appleton R. The role of lumbar puncture insuspected CNS infection—a disappearing skill? Arch Dis Child 2002;87:181-83.
45. Queensland Clinical Guidelines. Newborn hypoglycaemia. Guideline No. MN13.8-V5-R18. [Internet]. Queensland Health. 2013. [cited 1 September 2016]. Available from: http://www.health.qld.gov.au
46. Ainsworth SB. Neonatal formulary 7. Drug use in pregnancy and the first year of life. Wiley Blackwell BMJI Books 2015.
47. Queensland Clinical Guidelines. Neonatal stabilisation for retrieval. Guideline No. MN11.18-V1-R16. [Internet]. Queensland Health. 2011. [cited 1 September 2016]. Available from: http://www.health.qld.gov.au
48. Slaughter LA, Patel AD, Slaughter JL. Pharmacological treatment of neonatal seizures: A systematic review. J Child Neurol 2013;28(3):351-64.
49. Booth D, Evans D. Anticonvulsants for neonates with seizures. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004218 2004.
50. Bittigau P, Sifringer M, Ikonomidou C. Antiepileptic drugs and apotosis in the developing brain. Ann. N.Y Acad. Sci 2003;993:103-14.
51. Shetty J. Neonatal seizures in hypoxic–ischaemic encephalopathy – risks and benefits of anticonvulsant therapy. Developmental Medicine and Child Neurology 2015;57(Suppl. 3):40-3.
52. Donovan M, Griffin B, Kharoshankaya L, Cryan J, Boylan G. Pharmacotherapy for neonatal seizures: Current knowledge and future perspectives Drugs 2016;76:647-61.
53. Mathieson S, Livingstone V, Low Y, Pressler RM, Rennie J, Boylan G. Phenobarbital reduces EEG amplitude and propagation of neonatal seizures but does not alter performance of automated seizure detection. Clinical Neurophysiology 2016;127(10):3343-50.
54. Bartha A, Shen J, Katz K, Miscel R, Yap K, Ivacko J, et al. Neonatal seizures: multicenter variability in current treatment practices. Pediatric Neurology 2007;37(2):85-90.
55. Bassan H, Bental Y, Shany E, Berger I, Froom P, Levi L, et al. Neonatal Seizures: Dilemmas in Workup and Management. Pediatric neurology 2008;38(6):415-21.
56. Wickstrom R, Hallberg B, Bartocci M. Differing attitudes toward phenobarbital use in the neonatal period among neonatologists and child neurologists in Sweden. European Journal of Paediatric Neurology 2013;17:55-63.
57. Nagarajan L. Treatment of neonatal seizures In: Nagarajan L, editor. Neonatal seizures: current treatment and future challenges
London: MacKeith Press; 2016.
58. Micromedex Solutions. Paediatrics and Neofax [Internet]. 2016

59. Australian Medicines Handbook Children's Dosing Companion. Adelaide: Australian Medicines Handbook Pty Ltd; July 2016.
60. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: Safety and efficacy in neonatal seizures. European Journal of Paediatric Neurology 2011;15:1-7.
61. Kadam SD, Yu X, Johnston MV. Neuroprotective strategies for neonates with seizures. In: Nagarajan L, editor. Current management and future strategies. London: Mac Keith Press; 2016.
62. Filippi L, la Marca G, Fiorini P, Poggi C, Cavallaro G, Malvagia S, et al. Topirimate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic iscahemic encephalopathy. Epilepsia 2009;50(11):2355-61.
63. Schmitt B, Baumgartner M, Mills P, Clayton P, Jakobs C, Keller E, et al. Seizures and paroxysmal events: symptoms pointing to the diagnosis of pyridoxine-dependent epilepsy and pyridoxine phosphate oxidase deficiency. Developmental Medicine and Neurology 2010;52:e133-42.
64. Lombroso C. Neonatal seizures: gaps between the laboratory and the clinic. Epilepsia 2007;48(Suppl. 2):83-106.
65. Anand V, Nair P. Neonatal seizures: Predictors of adverse outcome. Journal of Pediatric Neurosciences 2014;9(May-August):97-9.
66. Darsaklis V, Snider L, Majnemar A, Mazer B. Predictive validity of Prechtl's method on the qualitative assessment of General Movements: a systematic review of the evidence. Developmental Medicine & Child Neurology 2011;53:896-906.
67. Morgan C, Crowie C, Goyen T, Hardman C, Jackman M, Novak I, et al. Sensitivity and specificity of General Movements Assessment for diagnostic accuracy of detecting cerebral palsy early in an Australian context. Journal of Paediatrics and Child Health 2016;52:54-9.
68. Walker K, Holland A, Halliday R, Badawi N. Which high-risk infants should we follow-up and how should we do it? Journal of Paediatrics and Child Health 2012;48:789-93.
69. Bosanquet M, Copeland L, Ware R, Boyd R. A systematic review of tests to predict cerebral palsy in young children. Developmental Medicine & Child Neurology 2013;55:418-26.

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

Queensland Clinical Guidelines F17.23-3-V1-R22 Neonatal seizures: Abnormal movements

Acknowledgements

Queensland Clinical Guidelines gratefully acknowledge the contribution of Queensland clinicians and other stakeholders who participated throughout the guideline development process particularly:

Working Party Clinical Lead
Professor Paul Colditz

QCG Program Officer
Ms Stephanie Sutherns

Working Party Members
Mrs Seija Argyros, Neonatal Nurse Practitioner, Royal Brisbane & Women's Hospital
Miss Angela Backen, Registered Nurse, Royal Brisbane & Women's Hospital
Mrs Maxine Ballinger, Clinical Nurse Consultant, Rockhampton Hospital
Mrs Josephine Bell, Registered Midwife, Stanthorpe Hospital
Mrs Rachael Berghuis, Clinical Nurse, Gold Coast University Hospital
Mrs Deb Byrt, Clinical Nurse Midwife, The Sunshine Coast Private Hospital
Ms Tanya Capper, Acting Head of Program (Midwifery), Central Queensland University
Ms Liz Chappell, Neonatal Nurse Educator, Gold Coast University Hospital
Dr Mark Davies, Neonatologist, Royal Brisbane & Women's Hospital
Dr Hazel Dobinson, Rural General Practitioner, Children's Health Queensland
Dr John Gavranich, Director of Paediatrics, Ipswich Hospital
Mrs Corne' Gouws, Clinical Nurse, Gold Coast University Hospital
Mr John Graham, Midwife, Caboolture Hospital
Ms Tina Gray, Clinical Nurse, Hervey Bay Hospital
Mrs Danielle Groves, Registered Nurse Midwife, Hervey Bay Hospital
Mrs Jodie Hole, Registered Nurse Midwife, Sunshine Coast Private Hospital
Ms Karen Hose, Neonatal Nurse Practitioner, Royal Brisbane & Women's Hospital
Dr Arif Huq, Paediatrician, Logan Hospital
Dr Peter Kopp, Paediatric Registrar, Gold Coast University Hospital
Ms Cathy Krause, Clinical Nurse and Midwife, St Vincent's Hospital Toowoomba
Mrs Nicole Lindenberg, Registered Nurse Midwife, St Vincent's Hospital, Toowoomba
Dr Stephen Malone, Paediatric Neurologist, Lady Cilento Children’s Hospital, Brisbane
Mrs Hayley McGillivray, Clinical Nurse, Hervey Bay Hospital
Dr Parvin Niknafs, Midwife, The Wesley Hospital, Brisbane
Ms Marian Rigney, Associate Nurse Unit Manager, Logan-Bayside Network
Mrs Erika Rossouw, Clinical Nurse, Gold Coast University Hospital
Dr Peter Schmidt, Director of Neonatology, Gold Coast University Hospital
Ms Alecia Staines, Consumer Representative, Maternity Consumer Network
Dr Lizelle Weber, Acting Director of Neonatology, Nambour Hospital
Dr Karen Whitfield, Senior Pharmacist, Royal Brisbane & Women's Hospital

Queensland Clinical Guidelines Team

Associate Professor Rebecca Kimble, Director
Ms Jacinta Lee, Manager
Ms Stephanie Sutherns, Clinical Nurse Consultant
Ms Cara Cox, Clinical Nurse Consultant
Dr Brent Knack, Program Officer
Steering Committee

Funding

This clinical guideline was funded by Healthcare Improvement Unit, Queensland Health