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Queensland Maternity and Neonatal **Clinical Guideline**

Neonatal seizures

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Contact:	Queensland Maternity and Neonatal Clinical Guidelines Program Email: MN-Guidelines@health.qld.gov.au URL: http://www.health.qld.gov.au/qcg

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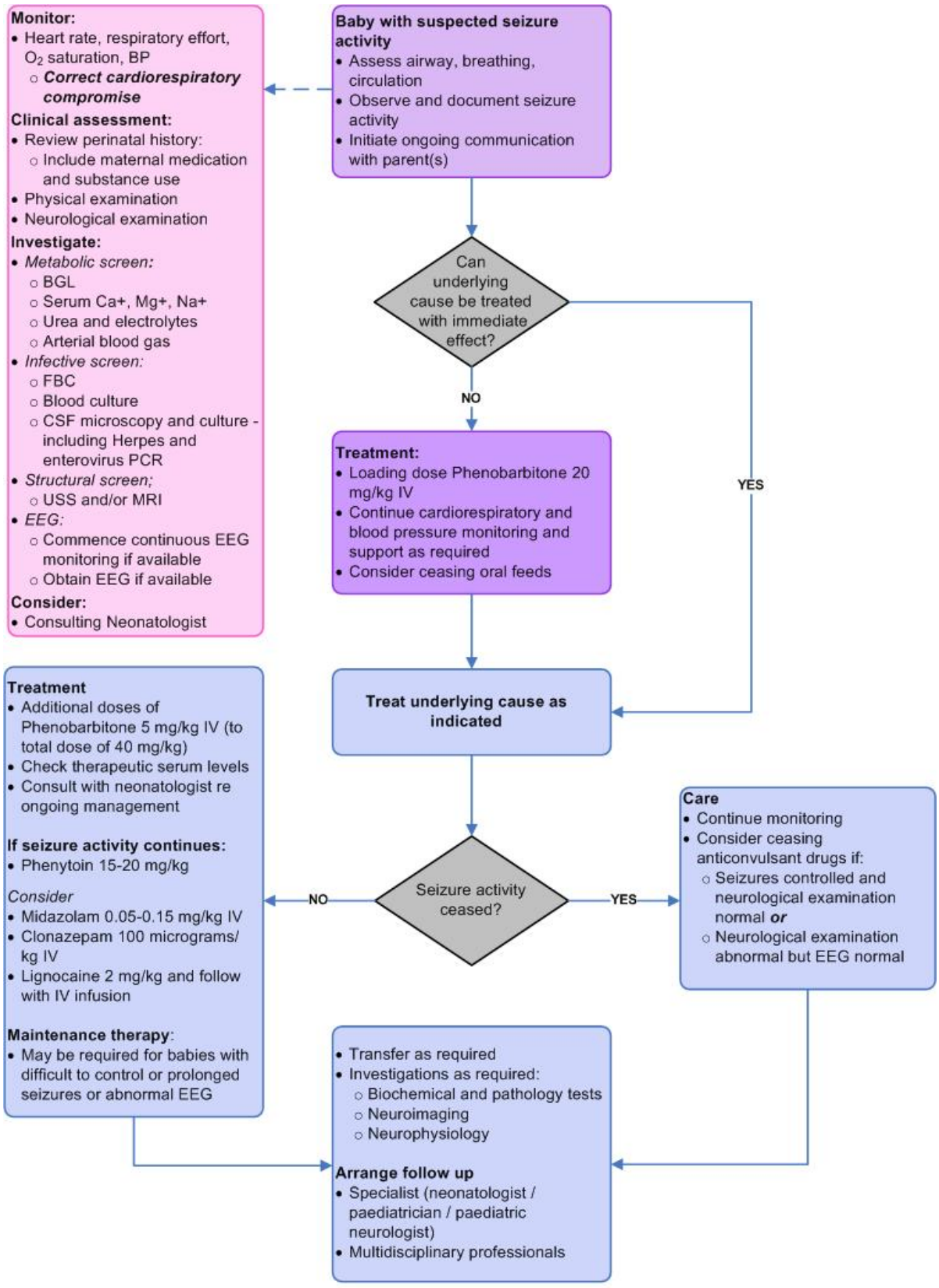
Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible to:

- Discuss care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary
- Advise consumers of their choice and ensure informed consent is obtained
- Provide care within scope of practice, meet all legislative requirements and maintain standards of professional conduct
- Apply standard precautions and additional precautions as necessary, when delivering care
- Document all care in accordance with mandatory and local requirements

Flow Chart: Neonatal seizure management



Queensland Maternity and Neonatal Clinical Guideline: MN11.23-V1-R16 Neonatal seizures

Abbreviations and acronyms

aEEG	Amplitude-integrated electroencephalograph
BGL	Blood glucose level
BP	Blood pressure
CSF	Cerebrospinal fluid
EEG	Electroencephalograph
HIE	Hypoxic-ischaemic encephalopathy
IM	Intramuscular
IV	Intravenous
IVH	Intraventricular haemorrhage
MRI	Magnetic resonance imaging
PVL	Periventricular leukomalacia
TORCH	**T**oxoplasmosis, **O**ther infections (hepatitis B, syphilis, herpes zoster, chickenpox) **R**ubella, **C**ytomegalovirus, **H**erpes simplex

Definition of terms

Apoptosis	A naturally occurring process that leads to cell death. It is normal in the developing brain in pruning unnecessary brain cells. Exaggerated apoptosis may occur with brain injury and has been reported with the use of anticonvulsants in animals.[1]

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1 Introduction

Neonatal seizures are a manifestation of neurological dysfunction.[2-7] Neonatal seizures are paroxysmal electroencephalograph (EEG) activity often with motor manifestations and sometimes with autonomic or behavioural clinical manifestations including effects on respiration, heart rate and blood pressure.[6] Frequent or prolonged seizures may contribute to a worsening of brain injury.[2,3,6,8-10]

Seizures may be an:

- Electro clinical seizure with both clinical signs and an EEG seizure[2], or an
- Electrographic seizure with no clinical signs[2]

Some apparent clinical seizure-like activity, e.g. jitteriness and irritability, is not associated with EEG abnormality. These are not seizures and do not require treatment.

1.1 Incidence

Seizures occur more frequently in the neonatal period (the first 28 days of life) than at any other time.[3-5,8,11] Incidence in the newborn baby is:

- 1.5-3.5 per 1000 live term births[2,3,6,11]
- 10-130 per 1000 live preterm births[6,11]
- Seizures are very common and occur in up to 70% of preterm infants with intraventricular haemorrhage or periventricular leukomalacia[12,13]
- Clinically diagnosed status epilepticus (continuous seizure activity or recurrent seizures lasting greater than 30 minutes[3,11] without definite return to the baseline neurologic condition between seizures[14]) is less common and occurs in only 5% of babies with seizures[3]
- Recognition is more frequent with the use of continuous EEG monitoring[3]

2 Major causes of neonatal seizures

There are many causes of neonatal seizures although only a few cause the majority of seizures.[4] [refer to Table 1. Major causes of neonatal seizures]

Table 1. Major causes of neonatal seizures

Cause	Comment
Hypoxic-ischaemic encephalopathy (HIE)[2,4-9,11,15]	• The most common cause in term infants[7,16] (40-60%[4,7,11]) and responsible for most babies with poor long term outcome[3,4,9,10] • Usually present within the first 24 hours[4] • Seizures may be difficult to control pharmacologically[4] • Therapeutic whole body cooling indicated in cases who meet specific criteria[17] • Refer to Guideline: Hypoxic-ischaemic encephalopathy[17]
Intracranial haemorrhage	• Intraventricular haemorrhage[4,7,11,15] • Intracerebral haemorrhage[4,7,11] • Subdural haemorrhage[4,7,11] • Subarachnoid haemorrhage[4,7,11]
Central nervous system infection	• Bacterial meningitis[2,4,5,7,11] • Viral meningitis[2,5,7,11] • Encephalitis • Intrauterine (TORCH) infections[2,4,5,7,11] • Most common bacterial pathogens are Group B Streptococcus, Escherichia coli, Listeria, Staphylococcus[4]
Perinatal stroke	• Arterial occlusion or venous thrombosis may result in stroke[2,4,5,9,11,15] • Incidence – 1 per 4000[9]
Metabolic	• Hypoglycaemia[2,4,7,9,11] • Hypocalcaemia[4,7,9,11] • Hypomagnesaemia[4,7,9,11] • Hypo/hypernatraemia[4,7,11] • Pyridoxine dependency[3]
Inborn errors of metabolism[2,4,7,9,11]	• Inborn errors of metabolism are a rare cause of seizure[4], however early investigation is essential in order to identify treatable causes[3]
Drug withdrawal syndromes[4,7,11]	• Refer to Guideline: Neonatal abstinence syndrome[18]
Congenital	• Chromosomal anomalies • Congenital brain anomalies[2,4,9] • Neuro-degenerative disorders
Benign idiopathic neonatal convulsions[4,7]	• 'Fifth day fits' usually multifocal clonic seizures occurring on the 5th day, generally ceasing within 15 days, the cause unknown[4]
Benign familial neonatal convulsions[4,9,11]	• Usually present as tonic or clonic seizures on Day 2 or 3[4,9] • Seizures cease after a few weeks and prognosis is good[4,9]
Idiopathic[4]	• Rarely idiopathic 2-5%[4]

3 Assessment

Assessment and diagnosis are made through a combination of clinical assessment including perinatal history, physical and neurological examinations, clinical observation, cardiorespiratory and electrographic monitoring:

- Discussion with a Neonatologist may be considered for guidance regarding assessment, diagnosis and management and the possible need for transfer:
    - The decision to transfer a baby should be determined by available resources at the referring hospital
    - Transfer to a higher level facility should be considered to ensure optimal outcome for any baby whose care requirement exceeds the facility's service capability
    - Consider the use of Telehealth, specifically video services, if available
    - Refer to Guideline: Neonatal Stabilisation[19]

3.1 Clinical observation

Traditionally, clinical observation has been the method used for seizure diagnosis.[3] However, clinical observation alone is unreliable as it may:

- Over detect apparent seizure activity that has no EEG correlate[3]
- Under detect clinical seizures with EEG correlates.[3] **The majority of electrographic seizures do not have overt clinical signs[20]**, known as electroconvulsive dissociation

3.2 Cardiorespiratory monitoring

Commence cardiorespiratory and blood pressure monitoring in babies:

- With encephalopathy at risk of or suspected of seizure activity. Alterations in autonomic functioning (e.g. blood pressure or heart rate) may represent seizure activity[2,3]
- Prior to administration of anticonvulsant drugs. Treatment may also be associated with alterations in autonomic functioning

Cardiorespiratory compromise may impair cerebral vascular autoregulatory capacity and predispose to secondary brain injury[20]:

- Ensure adequate airway and respiratory function:
    - Monitor heart rate, respiratory status, BP and oxygen saturation
    - Provide support if necessary
- Ensure intravenous access

3.3 Electrographic monitoring

Electrographic monitoring is recommended to confirm clinical seizures and detect electrographic seizures without clinical correlates.[2] The relationship between a clinical seizure and abnormal electrical activity is inconsistent.[2-4,9] For each type of monitoring, the longer the recording, the more useful it is likely to be. Electrographic monitoring is possible using[3]:

- 1-2 channel EEG, often interpreted using amplitude integrated EEG (aEEG)
- Conventional EEG, ideally accompanied by video

3.4 Documentation

For babies at risk of or with suspected seizure activity, document any episode of unusual or stereotypical movement and alterations in autonomic functioning. Information should include:

- The date, time and duration of each event
- Whether seizures are stereotypical with clear onset and offset
- Type (subtle, tonic, clonic, myoclonic and focal or generalised)
- Any abnormal eye movements
- Progression of events
- Any associated autonomic system changes (e.g. apnoea, hypotension, hypertension)
- Electrographic correlate (if there is concurrent electrographic monitoring)
- Any provoking stimulus (e.g. handling, noise)
- Whether they can be stopped or modified with posture or restraint (which makes them unlikely to be seizures)
- Response to administered medications

4 Differential diagnosis

Accurate seizure diagnosis remains a challenge. Any unusual or stereotypical movement may represent a seizure.[2,3] [refer to Table 3. Clinical classification of seizures]

4.1 Normal behaviour

Some normal behaviour of preterm and term babies may increase suspicion of seizures.[9] Normal behaviours include:

- Stretching, non-specific random movements that can be sudden (particularly in preterm babies), random sucking, coughing or gagging
- Physiological myoclonus known as benign neonatal myoclonus which occurs during active sleep (rapid eye movement (REM)) and quiet or non-REM sleep[21]

4.2 Jitteriness

Jitteriness occurs primarily in response to minor stimulation.[7] It is important to distinguish seizures from jitteriness.[7] [refer to Table 2. Differentiation between jitteriness and seizures]

Table 2. Differentiation between jitteriness and seizures

Sign[7]	**Jitteriness**[7]	**Seizure**[7]
Stimulus provoked[4]	Yes	No
Predominant movement	Rapid, oscillatory, tremor	Clonic, tonic
Movements cease when limb is held[4,9]	Yes	No
Conscious state	Awake or asleep	Altered
Eye deviation	No	Yes

4.3 Clinical seizure activity

Neonatal seizures can present in several ways and several types may be seen in the same baby over several hours.[3] Seizure activity is classified according to clinical presentation.[3,4,9] [refer to Table 3. Clinical classification of seizures for a summary of the four major types]

Table 3. Clinical classification of seizures

Seizure type	Proportion of neonatal seizures	Clinical signs
Subtle	• 10-35% depending on maturity[3] • More common in term babies • Occur in babies with severe global insult (e.g. HIE and intraventricular haemorrhage)[2]	• Eye – staring, blinking[9], horizontal deviation[7,9] • Oral – mouthing[3], chewing[7,9], sucking[7], tongue thrusting[3], lip smacking[3] • Limb – boxing, swimming movements of the arms[3], pedalling[3,7] • Autonomic – apnoea[3,7,9], tachycardia, unstable blood pressure[3]
Clonic	• 50%[3] • More common in term babies[7]	• Consciousness usually preserved • Rhythmic jerking (1-3/second) • Focal – limbs or one side of face or body.[7] May suggest underlying focal neuropathy (e.g. cerebral artery infarction) but can occur in metabolic disturbance • Multifocal – irregular, fragmentary, non-ordered migratory pattern[7]
Tonic	• 20%[3] • More common in preterm babies[7]	• May involve one extremity or the whole body • Generalised extension of upper and lower limbs with opisthotonic posturing[7] • Focal – sustained posturing of limb
Myoclonic	• 5%[3]	• Rapid isolated jerks[7] (distinguish from benign neonatal myoclonus) • Focal (one extremity) or multifocal (several body parts) • Seen in drug withdrawal (especially opiates)

5 Investigation

Investigation is required to determine the cause of seizures. Clues to cause may be present (e.g. history of perinatal asphyxia, maternal substance abuse) but other causes (e.g. hypoglycaemia, hypocalcaemia and central nervous system infection) may coexist and require exclusion.

5.1 Clinical assessment

- Review the perinatal history:
  - Family history of seizure, maternal drug use, maternal diabetes, antenatal and intrapartum infections, perinatal asphyxia, birth trauma
- Perform:
  - Physical examination (congenital anomalies, signs of sepsis)
  - Neurological examination

5.2 Pathology tests

Initial investigations recommended to determine cause include:

- Blood glucose level (BGL)[4,6,22]
- Serum electrolytes including calcium[22], magnesium,[22]
- Serum ammonia
- Full blood count[22]
- Blood cultures[4,6,22]
- Arterial blood gas[22]
- Serum amino acids
- Urine amino acids[4] and organic acids[4]
- Thrombophilia screen (after stroke)[9]
- Lumbar puncture – cerebrospinal fluid[6] microscopy and culture (bacterial and viral) [4,22]

Additional investigations may be required but will depend on the underlying cause, consider:

- Creatinine, liver function tests, drug screen, serum lactate, pyruvate
- Virology or congenital infection screen[4]
- Cerebrospinal fluid lactate, pyruvate, amino acids and neurotransmitters
- A trial of pyridoxine or pyridoxal phosphate treatment, preferably during EEG monitoring, may be diagnostic as well as therapeutic

5.3 Neuroimaging

- Cranial ultrasound scan[4,7,22] is recommended for all babies with seizures to exclude intracranial haemorrhage[7]
- Magnetic Resonance Imaging (MRI)[4,22] to evaluate the cause of seizures in preterm babies[15] and to provide the definitive diagnosis in term babies

5.4 Neurophysiology

- EEG[22] is the only way to identify electrographic seizures and to monitor response to therapy

6 Treatment – anticonvulsant drug therapy

The first treatment principle of treating the underlying cause is critical and may prevent further brain injury.[2] Seizures may not be controlled with antiepileptic drugs unless their underlying cause is treated [refer to Table 1. Major causes of neonatal seizures]. Aspects of anticonvulsant drug therapy for consideration are included below.

6.1 Evidence

Little evidence supports the use of any of the anticonvulsant drugs currently prescribed in the neonatal period[23] and there is lack of consensus regarding the optimal treatment protocol.[2,10] Early and accurate seizure detection is important for guiding anticonvulsant drug therapy[2]:

- Anticonvulsant drugs may not treat electroencephalographic seizures even if they are effective in reducing or eliminating the clinical manifestations (electro-clinical dissociation)[3,20,24]
- Commonly used anticonvulsant drugs may cause apoptosis in newborn animal models[1]:
    - This should not limit the appropriate use of anticonvulsant drug therapy [refer to Section 6.6 Anticonvulsant drug therapy schedules]

6.2 Initiation

Uncertainty exists over when to commence anticonvulsant drugs.[2] Anticonvulsant drugs should be considered to treat seizures after cause specific treatment when:

- Prolonged[3] – greater than 2-3 minutes[4]
- Frequent[3] – greater than 2-3 per hour[4]
- Disruption of ventilation and / or blood pressure homeostasis[4]

6.3 Administration

Administer anticonvulsant drugs:

- Intravenously to achieve rapid onset of action and predictable blood levels
- To achieve serum levels in the high therapeutic range
- To maximum dosage before introducing a second[3]

6.4 Maintenance and duration of treatment

The requirement for maintenance and duration of therapy is not well defined. The duration of anticonvulsant drug treatment should be as short as possible[3] however, this will depend on diagnosis and the likelihood of seizure recurrence.

- Maintenance therapy may not be required if loading doses of anticonvulsant drugs control clinical seizures
- Babies with prolonged or difficult to treat seizures and those with abnormality on EEG may benefit from continuing anticonvulsant treatment. If maintenance therapy is considered:
    - Serum levels should be monitored
    - Emergency seizure management plan should be developed, including, if required, a plan for buccal / intranasal Midazolam

6.5 Cessation of treatment

There is a low risk of seizure recurrence after early withdrawal of anticonvulsant in the neonatal period (e.g. following HIE).[25] Consider ceasing anticonvulsant drugs:

- Once seizures have ceased and the neurological examination is normal[3,4]
- If neurological examination remains abnormal, consider stopping if the EEG is normal

6.6 Anticonvulsant drug therapy schedules

The most commonly used anticonvulsant drugs are included in the sections below.

6.6.1 Phenobarbitone

Table 4. Phenobarbitone

Phenobarbitone	
Dose and administration	Loading dose: • 20 mg/kg IV[26,27,28] – administer over 10-15 minutes[26] • Optional additional doses of 5 mg/kg each until seizures cease or total dose of 40 mg/kg has been given[26] Maintenance: • IV (slow push – e.g.1 mg/kg/minute), IM, oral • 2.5-5 mg/kg[27] once daily beginning 12-24 hours after loading dose[26,27]
Comment	• First line treatment[2,3,9] • Effective in less than 50%[9] • Reduces clinically evident seizures but may have less effect on electrographic seizures[9,28] • Adding a second drug e.g. Phenytoin is often needed[26] • May cause apnoea/respiratory depression at high doses (40 mg/kg)[28] and high serum concentrations (above 60 microgram/mL)[26] • Significant age-dependent variation[29] in serum half life in neonates (40-200 hours)[26] • Second anticonvulsant drug may also increase serum concentration[26] Therapeutic range: • Measure trough levels 48 hours after IV loading dose • 15-40 microgram/mL (65-170 micromols/L)[26,30,31] • The above range reflects adult studies with recognition that there is wide variability, in therapeutic range, depending on age and type of seizure activity[29]

6.6.2 Phenytoin

Table 5. Phenytoin

Phenytoin	
Dose and administration	Loading dose[26]: • 15-20 mg/kg IV – maximum infusion rate of 0.5 mg/kg/minute Maintenance[26]: • IV (infusion rate – 0.5 mg/kg/minute) or oral • After loading dose: 4-8 mg/kg daily • After 1 week of age: Up to 8 mg/kg/dose – two or three times daily
Comment	• Not suitable for IM route[26] • Ensure integrity of IV due to potential for tissue inflammation and necrosis with extravasation[26] • Give IV through a filter always preceded and followed by a bolus of 0.9% Sodium Chloride[28] • Administer slowly IV to avoid cardiac dysrhythmia[26] • Monitor cardiac rate and rhythm and blood pressure for hypotension[26] • Avoid use in central lines due to the risk of precipitation[26] Therapeutic trough level[26]**:** • Measure trough levels 48 hours after IV loading dose • 6-15 microgram/mL in the first few weeks of life then 10-20 microgram/mL

6.6.3 Midazolam

Table 6. Midazolam

Midazolam	
Dose and administration	• 0.15 mg/kg IV over minimum of 5 minutes[26] Infusion: • 60-400 micrograms/kg/hour[26] • Reconstitution and dilution: o Dilute 1 mg/kg of Midazolam up to a total of 50 mL with 0.9% Sodium Chloride, 5% Glucose or 10% Glucose: ▪ 1 ml/hr = 20 micrograms/kg/hour
Comment	• May be effective in babies who continue seizures after Phenobarbitone and / or Phenytoin[3] • May cause significant respiratory depression and hypotension if injected rapidly, or used in conjunction with narcotics[26]

6.6.4 Clonazepam

Table 7. Clonazepam

Clonazepam	
Dose and administration	• 100 micrograms/kg[27] • IV push over 2 minutes or oral[27] • Repeat dose after 24 hours if necessary[27]
Comment	• Side effects - drowsiness, bronchial hypersecretion and increased salivation[27] • Sedative effect may mask cortical seizure activity that has not been suppressed[28] • May cause elevation in Phenytoin levels[27] • Concurrent treatment with Phenytoin reduces the half life of Clonazepam[28] • Avoid ampoules containing benzyl alcohol[27]

6.6.5 Lignocaine

Table 8. Lignocaine

Lignocaine	
Dose and administration	Loading dose[26]: • 2 mg/kg IV over 10 minutes, then commence an infusion Infusion[26]: • 6 mg/kg/hour for 6 hours, then o 4 mg/kg/hour for 12 hours, then ▪ 2 mg/kg/hour for 12 hours
Comment	• May be effective in babies who continue seizures after phenobarbitone[3] • **Do not give** to babies also treated with Phenytoin due to possible cardiac effects[26] • Continuous monitoring of heart rate and BP[26] • Only use preservative free ampoules without Adrenaline[26]

7 Parental support

Having a baby that is unwell is extremely stressful for parents and their families. It is recommended that:

- A family centred model of care with early Social Worker involvement provides support
- Early and ongoing communication is established with parent(s) to convey:
  - Information regarding baby's condition as soon as possible (information may have to be repeated as stress levels may affect information reception and retention)
  - Anticipated management plan and prognosis. This information should be delivered with honesty and sensitivity by the treating team. If the baby is not expected to survive, the parents should have an understanding of this
- Early communication with the Obstetric team to convey information regarding the baby's assessment, management plan and prognosis is necessary to facilitate consistent counselling for parents
- Document all communication regarding the management plan, prognosis and parental decisions to enable consistency of information transfer

7.1 Discharge documentation

Ensure the parents are provided with the appropriate discharge documentation:

- A seizure emergency management plan
- A copy of the discharge summary, including:
  - Types of seizures
  - Medications / Anticonvulsants administered
- Copies of referrals [refer to Section 8.1 Follow-up]

8 Prognosis

Prognosis is variable and dependent on underlying cause.[3,9,10,11] Some types of neonatal seizure are associated with high mortality[2] and poor long-term neurologic outcome.[2,5,6,8,9]

The results of neuroimaging and EEG give a better indicator of prognosis than clinical features alone[9]:

- Normal interictal EEG is associated with a good outcome[4]
- Normal neurological examination and normal / mildly abnormal EEG are associated with favourable outcome especially if neuroimaging is normal[11]
- Cerebral malformations[4] and severe hypoxia-ischaemia are associated with poor outcome[11]
- Babies with burst suppression or a markedly attenuated background pattern that persists for longer than 12 hours after birth are likely to have an adverse outcome[9]

8.1 Follow-up

Follow-up will depend on cause of seizure and response to treatment. Consider:

- Specialist (Neonatologist/Paediatric Neurologist) follow-up for babies discharged on anticonvulsant drugs
- General Paediatrician follow-up for all babies, in their local area
- Multidisciplinary follow-up to identify physical or cognitive deficit and provide timely neuro-rehabilitation intervention

9 Key points

- Almost any repetitive stereotypical movement pattern can be a manifestation of neonatal seizures[3]
- Frequent or prolonged seizures may cause long term neurodevelopmental problems
- Long duration video-EEG is the gold standard for diagnosis[3]
- Anticonvulsant drug therapy may cause electro-clinical dissociation (that is, the clinical seizures may disappear, but the electrical seizures continue) and the only way to confirm therapy effectiveness is by EEG monitoring[3]
- Anticonvulsant drug therapy is ineffective in controlling seizures in greater than 50% of cases[3]

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Professor Paul Colditz, Perinatal Medicine, University of Queensland

Working Party Members

Ms Maxine Ballinger, Clinical Nurse Consultant, Rockhampton Hospital

Dr Pita Birch, Neonatologist, Gold Coast Hospital

Ms Tanya Beaumont, Nurse Unit Manager, Neonatal Intensive Care Unit, Royal Brisbane and Women's Hospital

Mr Gregory Coulson, Neonatal Nurse Practitioner, Mackay Base Hospital

Dr Tim Donovan, Neonatal Paediatrician, Royal Brisbane and Women's Hospital

Ms Sharon Gilchrist, Clinical Nurse Consultant, Neurology, Royal Children's Hospital

Dr Timothy Hong, Neonatologist, Gold Coast Hospital

Ms Karen Hose, Clinical Nurse Consultant, Intensive Care Nursery, Royal Brisbane and Women's Hospital

Associate Professor Rebecca Kimble, Obstetrician, Royal Brisbane and Women's Hospital

Ms Claudia Konig, Pharmacist, Royal Brisbane and Women's Hospital

Ms Sam Lannan, Nursing Unit Manager, Special Care Nursery, Nambour Hospital

Dr Helen Liley, Neonatologist, Mater Health Services, Brisbane

Ms Teresa Mitchell, Clinical Nurse, Hervey Bay Hospital

Ms Megan Murphy, Clinical Nurse Consultant, The Townsville Hospital

Ms Jocelyn Neal, Midwifery Educator, Metro North District Service

Ms Jennifer Pye, Acting Clinical Network Coordinator, Central Maternity and Neonatal Network

Dr Peter Schmidt, Neonatologist, Gold Coast Hospital

Ms Mary Tredinnick, Pharmacist, Royal Brisbane and Women's Hospital

Professor David Tudehope, Neonatologist, Mater Hospital Brisbane

Ms Catherine van den Berg, Newborn Care Unit Project Manager, Gold Coast Hospital

Dr Judy Williams, Paediatrician, Bundaberg Hospital

Program Team

Associate Professor Rebecca Kimble, Director, Queensland Maternity and Neonatal Clinical Guidelines Program

Ms Jacinta Lee, Program Manager, Queensland Maternity and Neonatal Clinical Guidelines Program

Ms Jackie Doolan, Clinical Program Officer, Queensland Maternity and Neonatal Clinical Guidelines Program

Ms Lyndel Gray, Clinical Program Officer, Queensland Maternity and Neonatal Clinical Guidelines Program

Steering Committee, Queensland Maternity and Neonatal Clinical Guidelines Program

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