

Management of Neonatal Seizures

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Abstract

Seizures in the newborn period constitute a medical emergency. Subtle seizures are the commonest type of seizures occurring in the neonatal period. Myoclonic seizures carry the worst prognosis in terms of long-term neurodevelopmental outcome. Hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures. Multiple etiologies often co-exist in neonates and hence it is essential to rule out common causes such as hypoglycaemia, hypocalcemia, and meningitis before initiating specific therapy. A comprehensive evidence based approach for management of neonatal seizures has been described in this protocol.

Key words: Seizures, newborn, anti-epileptic therapy

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Introduction

Neonatal seizures (NS) are the most frequent and distinctive clinical manifestation of neurological dysfunction in the newborn infant. The incidence of NS is 2.8 per 1000 in infants with birth weights of more than 2500 g; it is higher in preterm low birth weight neonates – as high as 57.5 per 1000 in very low birth weight infants.¹ Infants with NS are at high risk of neonatal death or neurological impairment and epilepsy disorders in later life. Though, mortality due to NS has decreased over the years from 40% to about 20%, the prevalence of long-term neurodevelopment sequelae has largely remained unchanged at around 30%.² Improper and inadequate management of seizures could be one of the major reasons behind this phenomenon.

Definition

A seizure is defined clinically as a paroxysmal alteration in neurologic function, i.e. motor, behavior and/or autonomic function. This definition includes³:

1. Epileptic seizures: phenomena associated with corresponding EEG seizure activity
e.g. clonic seizures
2. Non-epileptic seizures: clinical seizures without corresponding EEG correlate e.g. subtle and generalized tonic seizures
3. EEG seizures: abnormal EEG activity with no clinical correlation.

Classification

Four types of NS have been identified¹ (Table 1):

Subtle seizures: They are called subtle because the clinical manifestations are mild and frequently missed. They are the commonest type and constitute about 50% of all seizures. Common examples of subtle seizures include:

1. *Ocular* - Tonic horizontal deviation of eyes or sustained eye opening with ocular fixation or cycled fluttering
2. *Oral–facial–lingual movements* - Chewing, tongue-thrusting, lip-smacking, etc.
3. *Limb movements* - Cycling, paddling, boxing-jabs, etc.
4. *Autonomic phenomena* - Tachycardia or bradycardia
5. *Apnea* may be a rare manifestation of seizures. Apnea due to seizure activity has an accelerated or a normal heart rate when evaluated 20 seconds after onset. Bradycardia is thus not an early manifestation in convulsive apnea but may occur later due to prolonged hypoxemia.

Clonic seizures: They are rhythmic movements of muscle groups. They have both fast and slow components, occur with a frequency of 1-3 jerks per second, and are commonly associated with EEG changes.

Tonic seizures: This type refers to a sustained flexion or extension of axial or appendicular muscle groups. These seizures may be focal or generalized and may resemble decerebrate (tonic extension of all limbs) or decorticate posturing (flexion of upper limbs and extension of lower limbs). Usually there are no EEG changes in generalized tonic seizures.

Myoclonic seizures: These manifest as single or multiple lightning fast jerks of the upper or lower limbs and are usually distinguished from clonic movements because of more rapid speed of myoclonic jerks, absence of slow return and predilection for flexor muscle groups. Common changes seen on the EEG include burst suppression pattern, focal sharp waves and hypsarrhythmia.

Myoclonic seizures carry the worst prognosis in terms of neuro-developmental outcome and seizure recurrence. Focal clonic seizures have the best prognosis.

Common causes of neonatal seizures^{1, 4-8}

The most common causes of seizures as per the recently published studies from the country are hypoxic ischemic encephalopathy, metabolic disturbances (hypoglycemia and hypocalcemia), and meningitis; the incidence of intraventricular hemorrhage was low in both the studies.^{7,8} Etiology could, however, vary between different centres depending upon the patient population (term vs. preterm), level of monitoring (only clinical vs. electrical and clinical seizures), etc.

Hypoxic-ischemic encephalopathy (HIE): HIE secondary to perinatal asphyxia is the commonest cause of NS. Most seizures due to HIE (about 50-65%) start within the first 12 hrs of life while the rest manifest by 24-48 hours of age. Additional problems like hypoglycemia, hypocalcemia, and intracranial hemorrhage may co-exist in neonates with perinatal asphyxia and these should always be excluded. Subtle seizures are the most common type of seizures following HIE.

Metabolic causes: Common metabolic causes of seizures include hypoglycemia, hypocalcemia, and hypomagnesemia. Rare causes include pyridoxine deficiency and inborn errors of metabolism (IEM).

Infections: Meningitis should be excluded in all neonates with seizures. Meningoencephalitis secondary to intrauterine infections (TORCH group, syphilis) may also present as seizures in the neonatal period.

Intracranial hemorrhage: Seizures due to subarachnoid, intraparenchymal or subdural hemorrhage occur more often in term neonates, while seizures secondary to intraventricular hemorrhage (IVH) occur in preterm infants. Most seizures due to intracranial hemorrhage occur between 2 and 7 days of age. Seizures occurring in a term 'well baby' on day 2-3 of life is often due to subarachnoid hemorrhage.

Developmental defects: Cerebral dysgenesis and neuronal migration disorders are rare

causes of seizures in the neonatal period.

Miscellaneous: They include polycythemia, maternal narcotic withdrawal, drug toxicity (e.g. theophylline, doxapram), local anesthetic injection into scalp, and phacomatosis (e.g. tuberous sclerosis, incontinentia pigmentii). Accidental injection of local anesthetic into scalp may be suspected in the presence of unilateral fixed and dilated pupil. Multifocal clonic seizures on the 5th day of life may be related to low zinc levels in the CSF fluid (benign idiopathic neonatal convulsions).

Seizures due to SAH and late onset hypocalcemia carry a good prognosis for long term neuro-developmental outcome while seizures related to hypoglycemia, cerebral malformations, and meningitis have a high risk for adverse outcome.

Approach to an infant with neonatal seizures^{1, 4-6}

1. History

Seizure history: A complete description of the seizure should be obtained from the parents/attendant. History of associated eye movements, restraint of episode by passive flexion of the affected limb, change in color of skin (mottling or cyanosis), autonomic phenomena, and whether the infant was conscious or sleeping at the time of seizure should be elicited. The day of life on which the seizures occurred may provide an important clue to its diagnosis. While seizures occurring on day 0-3 might be related to perinatal asphyxia, intracranial hemorrhage, and metabolic causes, those occurring on day 4-7 may be due to sepsis, meningitis, metabolic causes, and developmental defects.

Antenatal history: History suggestive of intrauterine infection, maternal diabetes, and narcotic addiction should be elicited in the antenatal history. A history of sudden increase in fetal movements may be suggestive of intrauterine convulsions.

Perinatal history: Perinatal asphyxia is the commonest cause of neonatal seizures and a detailed history including history of fetal distress, decreased fetal movements,

instrumental delivery, need for resuscitation in the labor room, Apgar scores, and abnormal cord pH (<7) and base deficit (>10 mEq/L) should be obtained. Use of a pudendal block for mid-cavity forceps may be associated with accidental injection of the local anesthetic into the fetal scalp.

Feeding history: Appearance of clinical features including lethargy, poor activity, drowsiness, and vomiting after initiation of breast-feeding may be suggestive of inborn errors of metabolism. Late onset hypocalcemia should be considered in the presence of top feeding with cows' milk.

Family history: History of consanguinity in parents, family history of seizures or mental retardation and early fetal/neonatal deaths would be suggestive of inborn errors of metabolism. History of seizures in either parent or sib(s) in the neonatal period may suggest benign familial neonatal convulsions (BFNC).

2. Examination

Vital signs: Heart rate, respiration, blood pressure, capillary refill time and temperature should be recorded in all infants.

General examination: Gestation, birth-weight, and weight for age should be recorded as they may provide important clues to the etiology – for example, seizures in a term 'well baby' may be due to subarachnoid hemorrhage while seizures in a large for date baby may be secondary to hypoglycemia. The neonate should also be examined for the presence of any obvious malformations or dysmorphic features.

CNS examination: Presence of a bulging anterior fontanel may be suggestive of meningitis or intracranial hemorrhage. A detailed neurological examination should include assessment of consciousness (alert/drowsy/comatose), tone (hypotonia or hypertonia), and fundus examination for chorioretinitis.

Systemic examination: Presence of hepatosplenomegaly or an abnormal urine odor may be suggestive of IEM. The skin should be examined for the presence of any neuro-cutaneous markers. Presence of hypopigmented macules or ash-leaf spot would be suggestive of tuberous sclerosis.

3. Investigations

Essential investigations: Investigations that should be considered in all neonates with seizures include blood sugar, serum electrolytes (Na, Ca, Mg), cerebrospinal fluid (CSF) examination, cranial ultrasound (US), and electroencephalography (EEG). CSF examination should be done in all cases as seizures may be the first sign of meningitis. It should not be omitted even if another etiology such as hypoglycemia is present because meningitis can often coexist. CSF study may be withheld temporarily if severe cardio-respiratory compromise is present or even omitted in infants with severe birth asphyxia (documented abnormal cord pH/base excess and onset within 12-24 hrs). An arterial blood gas (ABG) may have to be performed if IEM is strongly suspected.

One should carry out all these investigations even if one or more investigations are positive, as multiple etiologies may coexist, e.g. sepsis, meningitis and hypoglycemia.

Additional investigations: These may be considered in neonates who do not respond to a combination of phenobarbitone and phenytoin or earlier in neonates with specific features. These include neuroimaging (CT, MRI), screen for congenital infections (TORCH) and for inborn errors of metabolism.

Imaging: Neurosonography is an excellent tool for detection of intraventricular and parenchymal hemorrhage but is unable to detect SAH and subdural hemorrhage. It should be done in all infants with seizures. CT scan should be done in all infants where an etiology is not available after the first line of investigations. It can be diagnostic in subarachnoid hemorrhage and developmental malformations. Magnetic resonance

imaging (MRI) is indicated only if investigations do not reveal any etiology and seizures are resistant to usual anti-epileptic therapy. It can be diagnostic in cerebral dysgenesis, lissencephaly, and other neuronal migration disorders.

Electroencephalogram (EEG): EEG has both diagnostic and prognostic role in seizures. It should be done in all neonates who need anticonvulsant therapy. Ictal EEG may be useful for the diagnosis of suspected seizures and also for diagnosis of seizures in muscle-relaxed infants. It should be done as soon as the neonate is stable enough to be transported for EEG, preferably within first week. EEG should be performed for at least one hour.⁹ Inter-ictal EEG is useful for long-term prognosis of neonates with seizures. A background abnormality in both term and preterm neonates indicates a high risk for neurological sequelae. These changes include burst-suppression pattern, low voltage invariant pattern and electro-cerebral inactivity.

Amplitude integrated EEG: This new method provides continuous monitoring of cerebral electrical activity at the bedside in critically sick newborns. aEEG is helpful in evaluating the background as well in identification of seizure activity in neonatal seizures. As with conventional EEG, background abnormalities like burst-suppression or continuous low voltage pattern in aEEG also help in prognosticating the infant with seizures particularly in the setting of HIE. Seizure activity on aEEG is characterized by a rapid rise in both the lower and upper margins of the trace. Some seizures that are focal or relatively brief are, however, missed by this technique.¹

Screen for congenital infections: TORCH screen and VDRL should be considered in the presence of hepatosplenomegaly, thrombocytopenia, intrauterine growth restriction, small for gestational age, and presence of chorioretinitis.

Metabolic screen: This includes blood and urine ketones, urine reducing substances, blood ammonia, anion gap, urine and plasma aminoacidogram, serum and CSF lactate/

pyruvate ratio.

Management

1. Initial medical management:

The first step in successful management of seizures is to nurse the baby in thermoneutral environment and to ensure airway, breathing, and circulation (TABC). Oxygen should be started, IV access should be secured, and blood should be collected for glucose and other investigations. A brief relevant history should be obtained and quick clinical examination should be performed. All this should not require more than 2-5 minutes.

2. Correction of hypoglycemia and hypocalcemia:

If glucostix shows hypoglycemia or if there is no facility to test blood sugar immediately, 2 ml/kg of 10% dextrose should be given as a bolus injection followed by a continuous infusion of 6-8 mg/kg/min.

If hypoglycemia has been treated or excluded as a cause of convulsions, the neonate should receive 2 ml/kg of 10% calcium gluconate IV over 10 minutes under strict cardiac monitoring. If ionized calcium levels are suggestive of hypocalcemia, the newborn should receive calcium gluconate at 8 ml/kg/d for 3 days. If seizures continue despite correction of hypocalcemia, 0.25 ml/kg of 50% magnesium sulfate should be given intramuscularly (IM).

3. Anti-epileptic drug therapy (AED)¹

Anti-epileptic drugs (AED) should be considered in the presence of even a single clinical seizure since clinical observations tend to grossly underestimate electrical seizures (diagnosed by EEG) and facilities for continuous EEG monitoring are not universally available. If aEEG is being used, eliminating all electrical seizure activity should be the

goal of AED therapy.¹ AED should be given if seizures persist even after correction of hypoglycemia/ hypocalcemia (*Figure 1*).

3.1 Phenobarbitone (Pb)

It is the drug of choice in neonatal seizures. The dose is 20 mg/kg/IV slowly over 20 minutes (not faster than 1 mg/kg/min). If seizures persist after completion of this loading dose, additional doses of phenobarbitone 10 mg/kg may be used every 20-30 minutes until a total dose of 40 mg/kg has been given. The maintenance dose of Pb is 3-5 mg/kg/day in 1-2 divided doses, started 12 hours after the loading dose.

3.2 Phenytoin

Phenytoin is indicated if the maximal dose of phenobarbitone (40 mg/kg) fails to resolve seizures or earlier, if adverse effects like respiratory depression, hypotension or bradycardia ensue with phenobarbitone. The dose is 20 mg/kg IV at a rate of not more than 1 mg/kg/min under cardiac monitoring. Phenytoin should be diluted in normal saline as it is incompatible with dextrose solution. A repeat dose of 10 mg/kg may be tried in refractory seizures. The maintenance dose is 3-5 mg/kg/d (maximum of 8 mg/kg/d) in 2-4 divided doses. Oral suspension has very erratic absorption from gut in neonates, so it should be avoided. Thus only IV route is preferred in neonates and it should preferably be discontinued before discharge.

Fosphenytoin, the prodrug of phenytoin, does not cause the same degree of hypotension or cardiac abnormalities, has high water solubility (therefore can be given IM), and is less likely to lead to soft-tissue injury when compared with phenytoin. It is dosed in phenytoin equivalents (1.5 mg/kg of fosphenytoin is equivalent to 1 mg/kg of phenytoin).

3.3 Benzodiazepines

This group of drugs may be required in up to 15-20% of neonatal seizures. The

commonly used benzodiazepines are lorazepam and midazolam. Diazepam is generally avoided in neonates due to its short duration of action, narrow therapeutic index, and because of the presence of sodium benzoate as a preservative. Lorazepam is preferred over diazepam as it has a longer duration of action and results in less adverse effects (sedation and cardiovascular effects). Midazolam is faster acting than lorazepam and may be administered as an infusion. It causes less respiratory depression and sedation than lorazepam. However, when used as continuous infusion, the infant has to be monitored for respiratory depression, apnea, and bradycardia (*equipment for resuscitation and assisted ventilation should be available at the bedside of all neonates given multiple doses of AED*).

The doses of these drugs are given below:

Lorazepam: 0.05 mg/kg IV bolus over 2-5 minutes; may be repeated

Midazolam: 0.15 mg/kg IV bolus followed by infusion of 0.1 to 0.4 mg/kg/hour.

According to Volpe, the expected response of neonatal clinical seizures to anticonvulsants is 40% to the initial 20-mg/kg loading dose of phenobarbitone, 70% to a total of 40 mg/kg of Pb, 85% to a 20-mg/kg of phenytoin, and 95% to 100% to 0.05 to 0.1 mg/kg lorazepam.¹

3.4 Antiepileptic drugs for seizures refractory to above treatment

In exceptional circumstances when the seizures are refractory to the first-line AEDs, the following second-line drugs might be tried.

Lidocaine

It is usually administered as a bolus dose of 4mg/kg IV followed by an infusion rate of 2mg/kg/hr. It is tapered over several days. Adverse effects include arrhythmias, hypotension, and seizures. It should not be administered with phenytoin.

Paraldehyde

It may be used in seizures refractory to the first line drugs. A dose of 0.1-0.2 ml/kg/dose may be given IM or 0.3 ml/kg/dose mixed with coconut oil in 3:1 may be used by per rectal route. Additional doses may be used after 30 minutes and q 4-6 hourly. Adverse effects include pulmonary hemorrhage, pulmonary edema, hypotension, and liver injury.

Sodium valproate

It can be used for maintenance therapy in neonates. Per rectal route may be used in acute condition. IV preparation is now available. Dose is 20-25 mg/kg/d followed by 5-10 mg/kg every 12 hours. It should, however, be used with caution in newborns given the uncertain risk of hepatotoxicity following its use.

Vigabatrin

It has been used in neonates for refractory seizures, primarily for infantile spasms. The dose is 50 mg/kg/day.

Topiramate:

It shows promise in neonatal seizures because of its potential neuroprotective effect against injury caused by seizures. Topiramate has been used for refractory infantile spasms in infants. The higher volume of distribution compared with other drugs requires higher initial and maintenance doses of approximately 3 mg/kg.

3.5 Other therapies

Pyridoxine:

A therapeutic trial of pyridoxine is reserved as a last resort in refractory seizures. Intravenous route is the preferred method; however, suitable IV preparations are not universally available. Hence intramuscular (IM) route may have to be used (1 ml of neurobion has 50 mg pyridoxine and 1 ml each may be administered both the sides in either the gluteal region or anterolateral aspect of thigh). It should ideally be done in the NICU as hypotension and apnea can occur.

Exchange transfusion

This is indicated in life-threatening metabolic disorders, accidental injection of local anaesthetic, trans-placental transfer of maternal drugs (e.g. chlorpropamide), and bilirubin encephalopathy.

10.6 Maintenance anti-epileptic therapy

Principles of AED used in older children and adults are applicable to neonates also. Monotherapy is the most appropriate strategy to control seizures. Attempts should be made to stop all anti-epileptic drugs and wean the baby to only phenobarbitone at 3-5 mg/kg/day. If seizures are uncontrolled or if clinical toxicity appears, a second AED may be added. The choice may vary from phenytoin, carbamazepine, and valproic acid.

10.7 When to discontinue AED

This is highly individualized and no specific guidelines are available. We usually try to discontinue all medication at discharge if clinical examination is normal, irrespective of etiology and EEG. If neurological examination is persistently abnormal at discharge, AED is continued and the baby is reassessed at one month. If the baby is normal on examination and seizure free at 1 month, phenobarbitone is discontinued over 2 weeks. If neurological assessment is not normal, an EEG is obtained. If EEG is not overtly paroxysmal, phenobarbitone is tapered and stopped. If EEG is overtly abnormal, the infant is reassessed in the same manner at 3 months and then 3 monthly till 1 year of age (*Figure 2*). The goal is to discontinue phenobarbitone as early as possible.

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Table 1 Investigations required in a neonate with seizures

Essential investigations (required in all with few exceptions*)	Additional investigations
<ul style="list-style-type: none"> • Blood sugar • Serum Na, calcium, magnesium • Cerebrospinal fluid (CSF) examination • Cranial ultrasound (US) and • Electroencephalography (EEG) and/or amplitude integrated EEG 	<ul style="list-style-type: none"> • Hematocrit (if plethoric and/or at risk for polycythemia) • Serum bilirubin (if icteric) • Arterial blood gas and anion gap (lethargy, vomiting, family history, etc.) • Imaging: CT and/or MRI (if no etiology found after essential investigations) • TORCH screen for congenital infections • Work-up for inborn errors of metabolism

*Given in the text

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Figure 1 Acute management of neonatal seizures

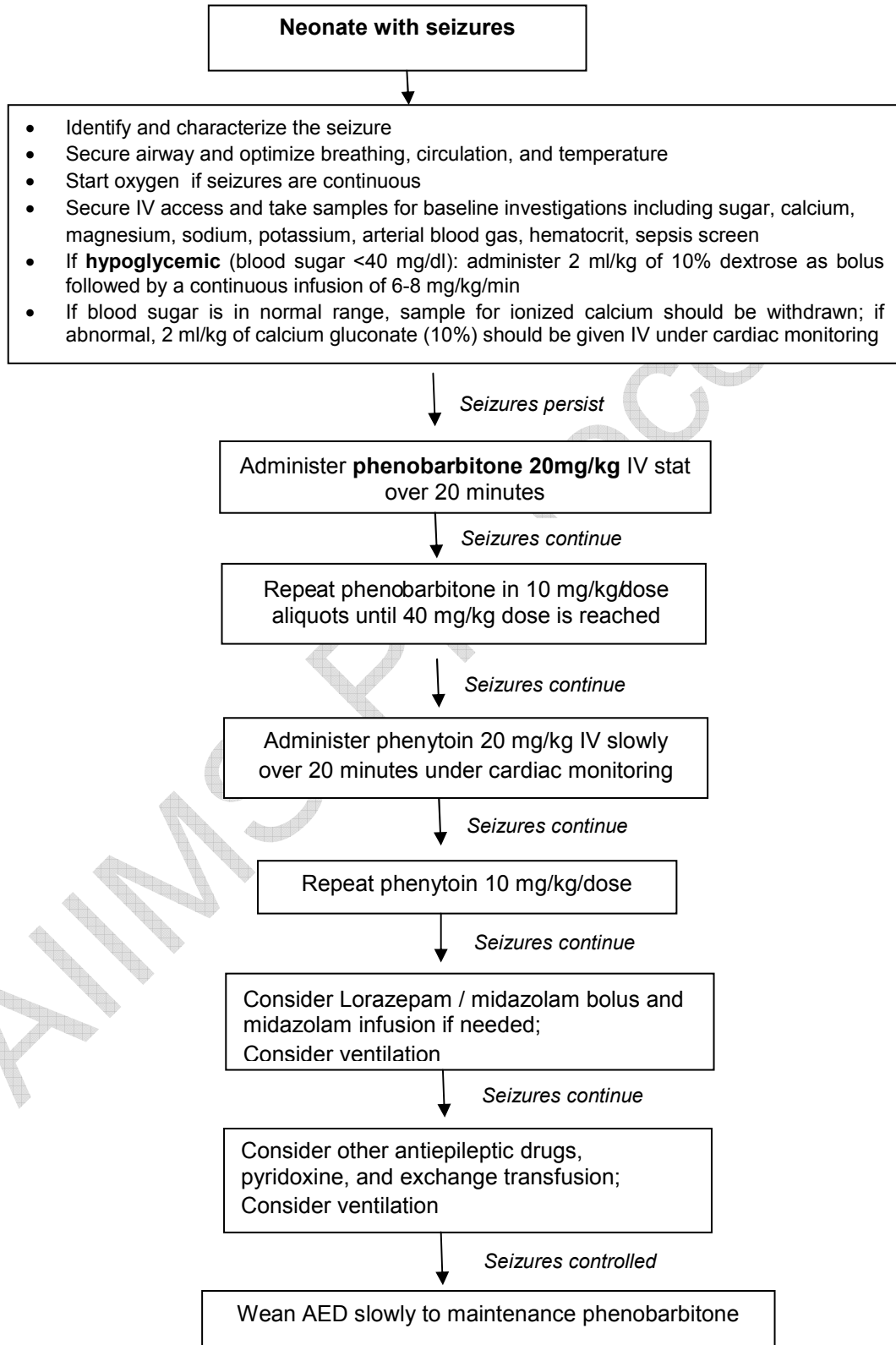
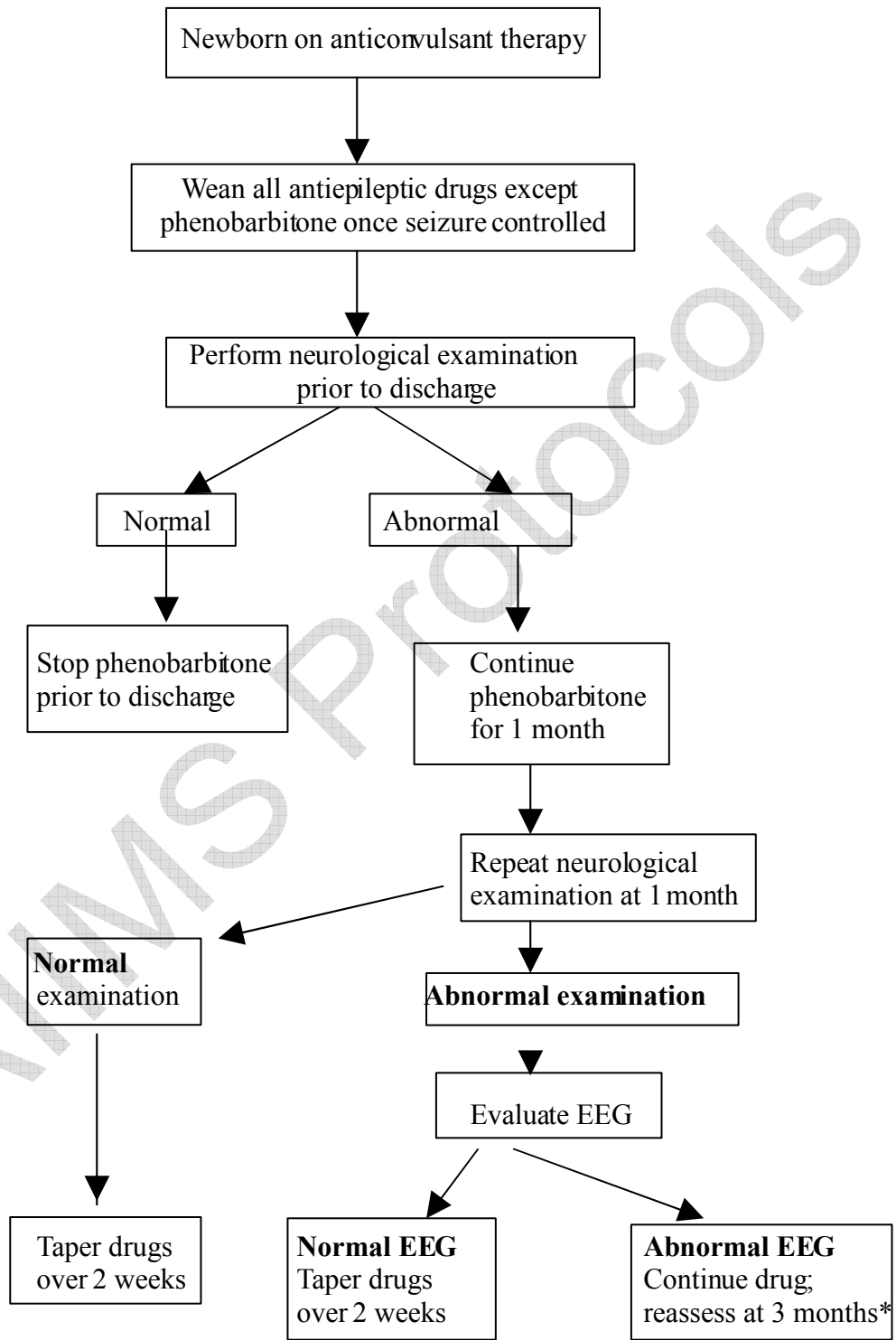


Figure 2 Weaning of anticonvulsant therapy



**Intractable seizures may need lifelong therapy; consider switching over to other drugs (phenytoin or carbamazepine)*