Management of Neonatal Seizures

Neonatal seizures (NS) are the most frequent and distinctive clinical manifestation of neurological dysfunction in the newborn infant. Infants with NS are at a high risk of neonatal death or neurological impairment/epilepsy disorders in later life. Though mortality due to NS has decreased from 40% to about 20% over the years, the prevalence of long-term neurodevelopment sequelae has largely remained unchanged at around 30%.[1] Improper and inadequate management of seizures could be one of the major reasons behind this phenomenon.

Epidemiology

The National Neonatal Perinatal Database (NNPD; 2002-03), which collected data from 18 tertiary care units across the country, has reported an incidence of 10.3 per 1000 live-births.[2] The incidence was found to increase with decreasing gestation and birth weight - for example, preterm infants had almost twice the incidence when compared to term neonates (20.8 vs. 8.4 per 1000 live-births) while very low birth weight infants had more than 4-fold higher incidence (36.1 per 1000 live-births).[2]

Definition

A seizure is defined clinically as a paroxysmal alteration in neurologic function, i.e. motor, behavior and/or autonomic function. This definition includes[4]:

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 major types of NS have been identified[3] (Table 1):

Subtle seizures: They are called subtle because the clinical manifestations are mild and are often missed. They are the commonest type, constituting 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, particularly in term infants. 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 neurodevelopmental outcome and seizure recurrence. Focal clonic seizures have the best prognosis.

Common causes of neonatal seizures[3, 5-9]

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.[8,9] 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 dependency 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 fixed and dilated pupil and absence of doll's eye reflex. 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[3, 6-7]

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 cow's 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 sodium and calcium, cerebrospinal fluid (CSF) examination, cranial ultrasound (US), and electroencephalography (EEG). CSF examination should be done in all cases as seizure may be the first sign of meningitis. It should not be omitted even if another etiology such as hypoglycemia is present. 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 of seizures within 12-24 hrs of life).

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 (IEM). An arterial blood gas may have to be performed if IEM is strongly suspected.

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.[10] 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 (aEEG): 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 NS. 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.[3]

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 serum 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.

3. Anti-epileptic drug therapy (AED)[3]

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

First-line AED: Evidence and recommendations

The Cochrane review found only one RCT that showed comparable seizure control rate with phenobarbital and phenytoin (RR 1.03, 95% CI 0.96 to 1.62), controlling seizures in only half of cases.[11]

Based on the available evidence, the WHO guidelines on neonatal seizures recommend phenobarbitone as the first-line agent for management of neonatal seizures.[12]

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 and should be avoided in neonates.

Fosphenytoin, the prodrug of phenytoin, does not cause the same degree of hypotension or cardiac abnormalities, has high water solubility (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 because of its short duration of antiepileptic effect but very prolonged sedative effect, narrow therapeutic index, and 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.

Second-line AED: Evidence and recommendations

The Cochrane review[11] found one study that randomized infants who failed to respond to phenobarbital to receive either lidocaine or midazolam as second-line agents. There was a trend for lidocaine to be more effective in reducing seizure burden (RR 0.40 95% CI 0.14 to 1.17) but both groups had similarly poor long term outcomes assessed at one year.

Based on the available evidence, the WHO guidelines on neonatal seizures recommend either midazolam or lidocaine as the second-line AED in neonatal seizures.[12]

However, given the lack of robust evidence and constraints involved in providing respiratory support and/or monitoring in most neonatal units in India, it seems appropriate to use phenytoin as the second-line agent in neonates with seizures.

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 control rate 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 phenobarbitone, phenyotin, and midazolam, the following drugs might be tried:

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

Paraldehyde: 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: Per rectal or IV route may be used in acute condition. The 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 with 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. It 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 injection 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 anesthetic, 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, carbamezepine, and valproic acid.

10.7 When to discontinue AED

This is highly individualized and no specific guidelines are available. The goal is to discontinue phenobarbitone as early as possible. We usually try to discontinue all medications 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)*.

Table 2 provides a brief list of the possible studies that could emanate from the identified research gaps.

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Table 1 **Investigations required in a neonate with seizures**

Essential investigations (required in all with few exceptions*)	***Additional investigations***
• Blood sugar • Serum sodium and calcium • Cerebrospinal fluid (CSF) examination • Cranial ultrasound (US) and • Electroencephalography (EEG) and/or amplitude integrated EEG	• Hematocrit (if plethoric and/or at risk for polycythemia) • Serum bilirubin (if icteric) • Serum magnesium • 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*

Table 2 Objectives and outcomes of possible studies

S. No	Title	Objectives	Possible outcome variables	Study design
1.	Epidemiology of neonatal seizures	To understand the epidemiology of seizures in term and preterm neonates in resource restricted settings	1. Incidence, etiology and type of neonatal seizures 2. Age at onset of seizures 3. EEG changes during ictal and inter-ictal periods 4. Outcomes of neonates with seizures	Cohort study (for incidence); Case-series for others
2.	First-line agent for treatment of neonatal seizures	To compare the seizure control rates following therapy with phenobarbitone with midazolam/lignocaine, newer drugs such leviteracetam, topiramate in neonates with convulsions	1. Seizure control rates (complete control as defined by EEG) 2. Time taken to achieve control of seizure episode 3. Duration of AED therapy and hospital stay 4. Neurodevelopment outcomes at 18-24 months age	Randomized trial
3.	Optimal second-line agent for treatment of neonatal seizures	To compare the seizure control rates following therapy with midazolam, lignocaine or levetiracetam in infants who failed to respond to phenobarbital therapy	Same as above	Randomized trial
4.	Discontinuing AEDs in neonates with seizures	To determine the optimal timing and method of discontinuation of AEDs in newborns whose seizures are controlled on current AED treatment (for e.g. stopping AED after 72 hours vs. after 2-4 weeks; abrupt stoppage of phenobarbitone vs. gradual tapering followed by stopping)	1. Seizure recurrence 2. Neurodevelopment outcomes at 18-24 months age	Randomized trial/ cohort study

Figure 1 Acute management of neonatal seizures

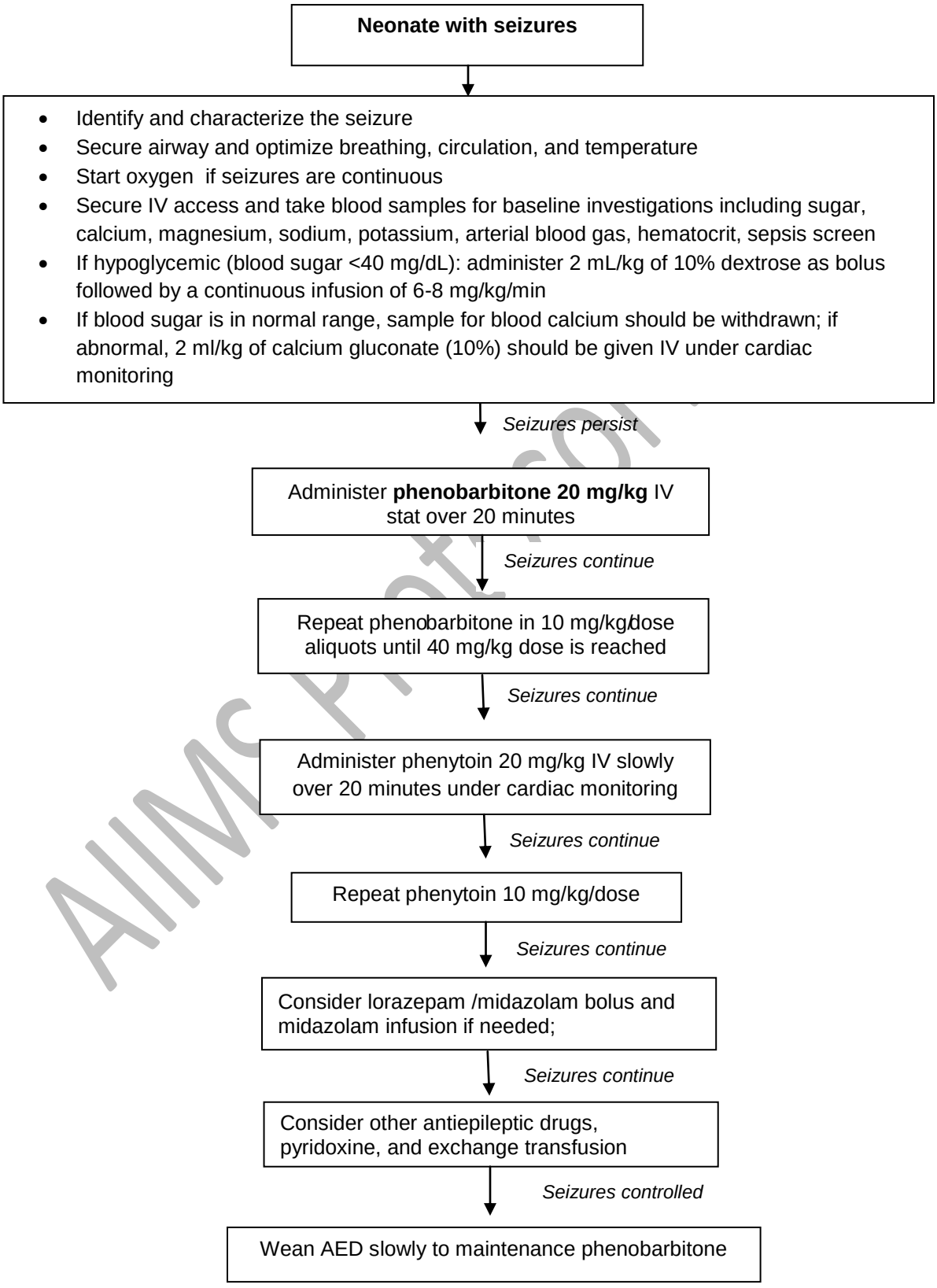
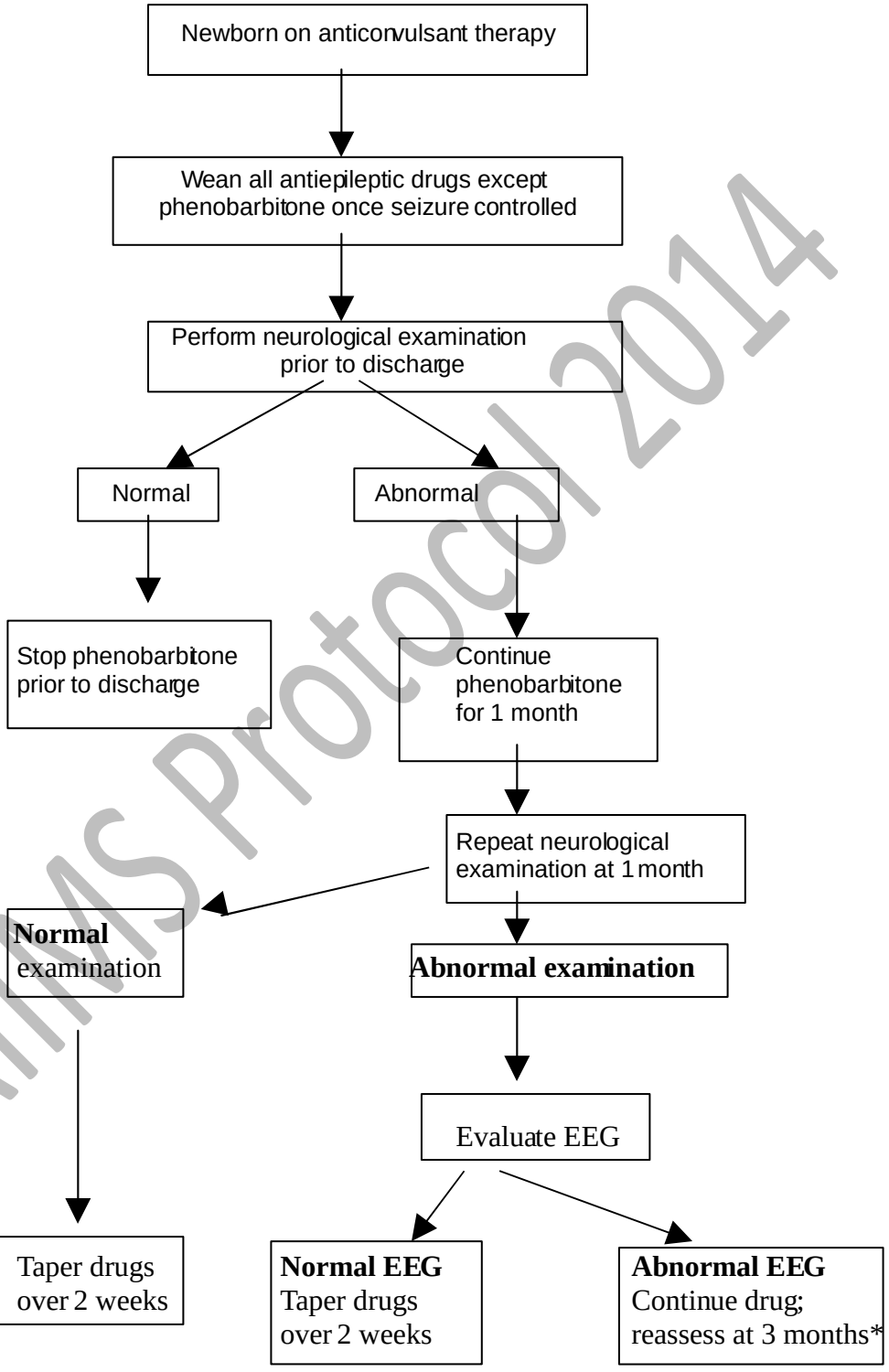


Figure 2 Weaning of anticonvulsant therapy



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