Seizures in Neonates

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seizures are a common and important clinical manifestation of neurologic dysfunction in the newborn.

The incidence of seizures varies with gestational age and birth weight and is most common in the very low birth weight (VLBW) infant.

A seizure results from an excessive synchronous electrical discharge .

(i.e., depolarization) of neurons within the central nervous system.

Pathophysiology

It is important to understand that in the vast majority of neonatal seizures, electrical onset is focal or multifocal, with the spread of the seizure occurring within one hemisphere and secondary generalization to the contralateral hemisphere occurring only rarely.

Thus newborns rarely have well organized, generalized, tonic-clonic seizures, and premature infants have even less well-organized seizures than do term infants.

Excitatory activity is mediated by glutamate through two key receptor types:

- *N*-methyl-d-aspartate (NMDA)
- alpha-amino-3-hydroxy-5-methyl- 4-isoxazolepropionic acid (AMPA).

- In addition, early in development, the principal inhibitory neurotransmitter, GABA, acts at the major postsynaptic GABAA receptor (GABAA) to produce excitation rather than inhibition, as occurs later in development.

- Moreover, because the maturation of the two cotransporters and neuronal Cl^- levels occurs in a caudal-rostral direction, spinal cord and brainstem motor neurons would be expected to exhibit GABA-mediated inhibition before the cerebral cortical regions.

- This maturational process could explain the frequent occurrence of electroclinical uncoupling/dissociation in which antiseizure medications with GABA agonist mechanisms (i.e., phenobarbital and benzodiazepines) suppress motor manifestations of seizures (by spinal cord and brainstem inhibition) but not cortical EEG manifestations (due to lack of cortex inhibition).

The deleterious effects of seizures may be divided into:

- those related to prolonged seizures (most prominent feature is cell loss)
- those related to briefer recurrent seizures (most prominent feature is altered development).

Importantly, although the threshold for seizure generation is lower in the developing brain than in the mature brain, developing neurons are less vulnerable to injury from single prolonged seizures than are mature neurons. This may be due to:

- a lower density of active synapses
- lower energy consumption
- immaturity of relevant biochemical cascades to cell death.

Classification of Seizures in the Newborn

- A seizure is defined clinically as a paroxysmal alteration in neurologic function (i.e., behavioral, motor, or autonomic)

Neonatal Seizures classifies two types of seizures:

1) electroclinical seizures, in which there is a clinical seizure coupled with an associated EEG seizure

2) electrographic- only seizures, in which there is an EEG seizure that is not associated with any outwardly visible clinical signs.(subclinical, nonconvulsive, or occult seizures)

Neonatal EEG seizures are described as having :

- a sudden EEG change
- Repetitive waveforms that evolve in morphology, frequency, and/or location
- amplitude of at least 2 microvolts
- duration of at least 10 seconds.
- seizures must be separated by at least 10 seconds to be considered separate
- clinical signs may or may not be present

- It is normal for newborns to have some sharp waves, and many newborns with epileptiform discharges do not experience seizures.

However, epileptiform discharges that occur in runs or are clustered in one brain region are associated with an increased risk of seizure occurrence.

Seizure Types

- *Seizures With Automatisms:*
- Seizures with automatisms involve activities of coordinated motor activity which can appear voluntary in nature.

- include ocular movements, oral-buccal-lingual movements, a progression movements of the limbs such as pedaling, swimming, and rowing.
- Movements can be unilateral, bilateral, and asymmetric or bilateral and symmetric.

As these movements can mimic normal neonatal behavior, EEG monitoring is required to assess if the event is ictal.

Seizures with automatisms can be seen in patients with hypoxic-ischemic encephalopathy as well as preterm infants.

Ocular movement:

term : eye opening with ocular fixation

preterm: horizental deviation

- *Clonic Seizures* :

A clonic seizure is defined as a seizure characterized by “rhythmic movements of muscle groups in a focal distribution, which consist of a rapid phase followed by a slow return movement.”

- Clonic seizures appear as repetitive and rhythmic jerking movements that can affect any part of the body, including the face, extremities, and even diaphragmatic or pharyngeal muscles.

- Clonic seizures represent the clinical seizure type associated most consistently with EEG seizure activity.

Clonic seizures in the newborn are often classified as focal or multifocal. Focal clonic seizures involve the face, upper or lower extremities on one side of the body, or axial structures (neck or trunk) on one side of the body.

- Newborns commonly are not clearly unconscious during or after a focal seizure.

- The neuropathologic condition often is focal (e.g., cerebral infarction), although focal clonic seizures may occur with metabolic encephalopathies.

- Clonic seizures are often reliably recognized by clinical observation, but they must be distinguished from other repetitive movements such as jitteriness, tremulousness, and myoclonus.

- Multifocal clonic seizures involve several body parts, often in a migrating fashion.

- *Tonic Seizures:*

Tonic seizures are defined as a “sustained flexion or extension of axial or appendicular muscle groups.”

- Two categories of tonic seizures should be distinguished:
  focal and generalized tonic seizures.

- Focal tonic seizures consist of sustained posturing of a limb or asymmetrical posturing of the trunk or neck.

- Mizrahi and Kellaway also classified horizontal eye deviation as a focal tonic seizure, although some classify those events as subtle seizures.

➢ *Focal tonic seizures are associated consistently with EEG seizure discharges.*

- Generalized tonic seizures are characterized by tonic extension of both upper and lower extremities. (mimicking “decerebrate” posturing) but also by tonic flexion of upper extremities with extension of lower extremities (mimicking “decorticate” posturing).

- The possibility that such clinical seizures represent posturing and are not ictal has been raised because of the frequent association with severe intraventricular hemorrhage (IVH) and the often poor response to antiseizure medication therapy.

- *Approximately 85% of such clinical seizures were not accompanied by electrographic activity or by autonomic phenomena.*

- The 15% of generalized tonic seizures that were accompanied by electrographic seizure activity were also accompanied by autonomic phenomena.

- hyperekplexia: episodes of generalized hypertonia provoked

by minor tactile or other stimuli.

Myoclonic Seizures:

- Myoclonus is defined as a rapid, isolated jerk that can affect one or multiple muscle groups.
- can be ictal or non ictal in etiology, and can arise from injury to any level of the nervous system.

➢ *Myoclonic seizures are clinical episodes that are usually not associated with EEG discharges.*

Myoclonic movements are distinguished from clonic movements by the faster speed of the myoclonic jerk and the predilection for flexor muscle groups.

There are three categories of myoclonic seizures: focal, multifocal, and generalized myoclonic seizures.

- Focal myoclonic seizures typically involve flexor muscles of an upper extremity.

- Multifocal myoclonic seizures are characterized by asynchronous twitching of several parts of the body.
- Generalized myoclonic seizures are characterized by bilateral jerks of flexion of upper and occasionally of lower limbs.
- These seizures may appear identical to the infantile spasms observed in older infants.
- Generalized myoclonic seizures are more likely to be associated with EEG seizure discharges than are focal or multifocal myoclonic seizures.

All three varieties of myoclonic seizures may occur as a feature of severe neonatal epileptic syndromes.

Myoclonic seizures must be distinguished from nonepileptic myoclonus, which can occur with injury to any level of the nervous system and from normal physiologic myoclonus.

- Unlike such other forms of myoclonus, myoclonic seizures are not induced by stimuli and cannot be suppressed by pressure to the affected body part.

- Furthermore, newborns with myoclonic seizures almost always have abnormal neurologic exams, whereas newborns with benign myoclonus are otherwise normal.

Epileptic Spasms:

Epileptic spasms involve proximal and truncal muscles that suddenly flex, extend, or both.

- can be unilateral, bilateral and asymmetric, or bilateral and symmetric.
- will last longer than a myoclonic seizure but not as long as a tonic seizures.

- Subtle forms of spasms include grimacing, head nodding, or subtle eye movements.

- Epileptic spasms are rare and are seen in patients with metabolic disorders and infantile developmental and epileptic encephalopathies.

- *Autonomic Seizures:*

Seizures with autonomic features involve alterations of the autonomic nervous system including the cardiovascular, gastrointestinal, sudomotor, vasomotor, pupillary, and thermoregulatory functions.

- Etiologies include : intraventricular hemorrhages and temporal or occipital lobe lesions, as well as infantile developmental and epileptic encephalopathies.

- *Autonomic seizures can involve apnea.*

- *apnea has been documented with electrical seizure activity, more commonly in the full-term newborn.*

- *apnea accompanied by EEG seizure activity (i.e., convulsive apnea) is less likely to be associated with bradycardia than is nonconvulsive apnea.*

- *Seizures With Behavioral Arrest:***

Seizures with behavioral arrest can appear as an arrest or freezing of activities.

They are rare as an isolated seizure type and are more commonly seen as part of a sequential seizure.

- *Sequential Seizure and Unclassified Seizure Type:*

Sequential seizures do not have a predominant feature. The seizure can present with a variety of different signs occurring in a sequence.

- The EEG can show changing lateralization within or between seizures.

- This type of seizure is often seen in genetic epilepsies.

- *EEG-Only (Subclinical, Nonconvulsive, Occult) Seizures:*

A major issue with clinical diagnosis of seizures in newborns is the high incidence of EEG-only seizures in newborns.

Numerous studies have indicated that about 80% to 90% of electrographic seizures do not have any associated clinical correlate and therefore would not be identified without continuous EEG monitoring.

- *Nonepileptic Movements:*

- can be difficult to distinguish from seizures by appearance alone, and EEG assessment may be required.

Some nonictal movements are benign events while others, although not seizures, are nonetheless abnormal and indicative of underlying brain injury or dysfunction.

- Jitteriness: Jitteriness is characterized by movements with qualities primarily of tremulousness but occasionally of clonus.

- The most consistently defined causes of jitteriness are hypoxicischemic encephalopathy (HIE), hypocalcemia, hypoglycemia, and drug withdrawal.

TABLE 57.1 Distinguishing Between Jitteriness and Seizure

Clinical Feature	Jitteriness	Seizure
Abnormality of gaze or eye movement	0	+
Movements stimulus sensitive	+	0
Predominant movement	Tremor	Clonic jerking
Movements cease with passive flexion	+	0
Associated autonomic changes	0	+

0, Absent; +, present.

Tremor: (the alternating movements are rhythmic and of equal rate and amplitude, typically high-frequency and low amplitude movements)

clonic jerking : (movements with a fast and slow component with a frequency typically ranging from 1 to 3Hz with decreasing frequency and increasing amplitude as the seizure moves forward in time).

- Nonepileptic Myoclonus:
  - may be benign or pathologic.

  - Benign neonatal myoclonus, alternately termed benign neonatal sleep myoclonus, can be pronounced, typically is most prominent in sleep, and can last up to several minutes.

❖ Benign myoclonus can be stopped by rousing the infant and typically does not involve the face.

- usually last for several minutes or more and occur only during sleep, particularly quiet (non–rapid eye movement) sleep.

- They can be provoked by gentle rocking of the crib mattress in a head-to-toe direction and cease abruptly with arousal.

- The episodes can be exacerbated or provoked by treatment with benzodiazepines and resolve within approximately 2 months.

- Pathologic Myoclonus:

is attributed to a brainstem release phenomenon from loss of cortical inhibition of lower circuits.

- It is frequently seen in infants with severe global brain injury from hypoxia-ischemia, severe IVH, and toxic-metabolic disturbances, including drug withdrawal and glycine encephalopathy.

- These newborns have abnormal neurologic exams and abnormal background patterns on EEG.

- Hyperekplexia:

Hyperekplexia is also known as startle disease or congenital stiff-man syndrome.

- It is characterized principally by two abnormal forms of response to unexpected auditory, visual, and somesthetic stimuli—an exaggerated startle response and sustained tonic spasms.

- Additional features are generalized hypertonia and prominent nocturnal myoclonus.

The “minor” form of hyperekplexia only involves excessive startle.

the “major” form is associated with additional problems, including generalized stiffness while awake, nocturnal myoclonus, and an increased risk of sudden infant death syndrome from apnea.

- Hyperekplexia may be caused by glycine receptor gene mutations.
- clonazepam can be an effective treatment for excessive startle.
- The episodes usually cease spontaneously by approximately the age of 2 years.

Does Absence of EEG Seizure Activity Indicate That a Clinical Event Is Nonepileptic?

- epileptic phenomena can occur in the absence of surface-recorded EEG discharges, and such phenomena can be generated at subcortical (i.e., deep limbic, diencephalic, brainstem) levels.

- Thus one should continue to use some aspect of clinical judgment in the decision-making process of trials of anticonvulsant therapy or consider electroencephalographic silence as a key indicator of abnormality in a high-risk newborn.

Seizure Etiology

TABLE 57.2 **Neonatal Seizure Etiologies in Relation to Time of Seizure Onset and Relative Frequency**

	Time of Onset		Relative Frequency[a]	
Cause	0–3 Days	>3 Days	Premature	Full Term
Hypoxic-ischemic encephalopathy	+		+++	+++
Cerebrovascular stroke	+		+	+++
Intracranial hemorrhage	+	+	++	+
Intracranial infection	+	+	++	++
Developmental defects	+	+	++	++
Hypoglycemia	+		+	+
Hypocalcemia	+	+	+	+
Other metabolic	+			+
Epilepsy syndromes	+	+		+

[a]Relative frequency of seizures: +++, most common; ++, less common; +, least common.

Diagnosis

The first laboratory tests to be performed are directed against the two disorders that are dangerous but readily treated when recognized promptly:

- hypoglycemia and bacterial meningitis.
- blood should be drawn for determinations of Na+, K+, calcium, phosphorus, and magnesium levels.
- Other imaging and laboratory studies should be directed by specific clinical features.

- Focal seizures should lead to neuroimaging because of the frequency of focal ischemic cerebral lesions, and MRI is preferred.

- the most common etiologies of neonatal seizures are HIE, intracranial hemorrhage, and perinatal arterial ischemic stroke.

Warning signs for inborn errors of metabolism as a cause of neonatal seizures include:

(1) seizures beginning in the antepartum period

(2) seizures refractory to anticonvulsant medications

(3) progressive worsening of clinical and electroencephalographic abnormalities

(4) EEG showing burst suppression

(5) MRI showing prominent brain atrophy

(6) findings of HIE without any obvious hypoxic-ischemic event identified.

- low CSF glucose but normal blood glucose should suggest glucose transporter defect.
- the presence of elevated CSF glycine despite normal blood amino acids should suggest transient or true nonketotic hyperglycinemia.
- presence of elevated CSF lactate should suggest a mitochondrial disorder.
- When clinically appropriate, genetic testing should be employed for assessment and/or confirmation of suspected genetic conditions.

Electroencephalogram and Electroencephalographic Monitoring

- important diagnostic and prognostic information.

(1) electrodes be placed using the International 10-20 system with additional electrocardiogram, respiratory, eye, and electromyography leads.

(2) at least 1 hour of recording to adequately assess cycling through wakefulness and sleep.

(3) high-risk newborns be monitored for at least 24 hours to screen for the presence of electrographic seizures.

(4) in newborns with seizures, for monitoring to occur during seizure management and for an additional 24 hours after the last electrographic seizure.

- Amplitude-Integrated EEG

- The primary advantages of aEEG relate to its relative ease of use.


Review
ADMIN
08:31:35 Thu 20 Nov
Total: 19:41
EEG Waveform Left
EEG Waveform Right
50
µV
25
0
-25
-50
-5
-4
-3
-2
-1
+1
+2
+3
+4
+5
XC
BL
EEG
10s
1m
10m
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aEEG Right
100
µV
10
5
0
06:05
Thu 20 Nov
07:05
06:05
09:05
09:26
Check Signal
Mark Event
Change Index
Exit Review
Tools

Prognosis

TABLE 57.5 Prognosis of Neonatal Seizures: Relation to Neurologic Disease

Neurologic Disease[a]	Normal Development[b]
Hypoxic-ischemic encephalopathy	50%
Intraventricular hemorrhage[c]	10%
Primary subarachnoid hemorrhage	90%
Hypocalcemia	
Early-onset	50%[d]
Later-onset	100%[e]
Hypoglycemia	50%
Bacterial meningitis	50%
Developmental defect	0%

[a]Prognosis is for those cases with the stated neurologic disease when seizures are a manifestation.
[b]Values are rounded off to the nearest 5%.
[c]Usually, severe intraventricular hemorrhage.
[d]Typically in the first 72 hours of life.
[e]After 7 days of life.

- *Relation of EEG to Outcome:*

EEG background and quantitation of seizure burden.

- Most newborns with seizures occurring on a normal EEG background generally have a normal outcome.

- The burst-suppression pattern is particularly typical of the newborn with severe bilateral cerebral disease and is characterized by relatively long periods of voltage suppression (<5 μV) or by no electrical activity at all in the intervals between the bursts of activity.

- Consideration of the impact of sedating medications on the EEG background is important.

- because EEGs may evolve over time, repeat EEG tracings may be useful.

Management

Selection of Whom to Treat:

- Why should the infant with seizures be treated with anticonvulsant medication at all?

The answer relates to the potential adverse effects of seizures on ventilatory function, circulation, cerebral metabolism, and subsequent brain development.

- repeated seizures should be stopped.

- The World Health Organization guideline on neonatal seizures recommended treatment of all clinical and electrographic seizures.

Adequacy of Treatment

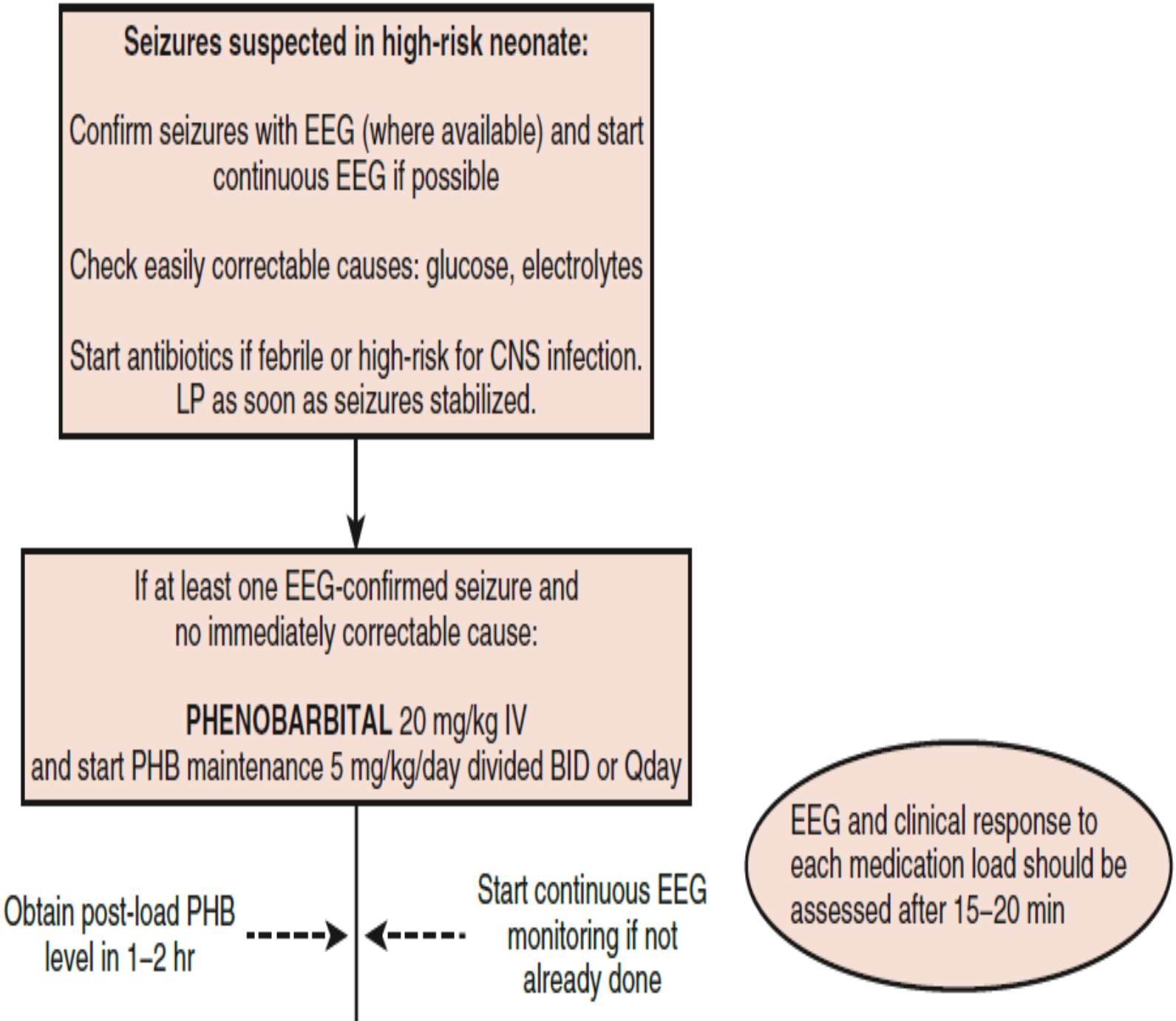
- The goal of therapy is the elimination of electrical seizure activity, based on the fact that many seizures in the newborn infant are clinically silent.

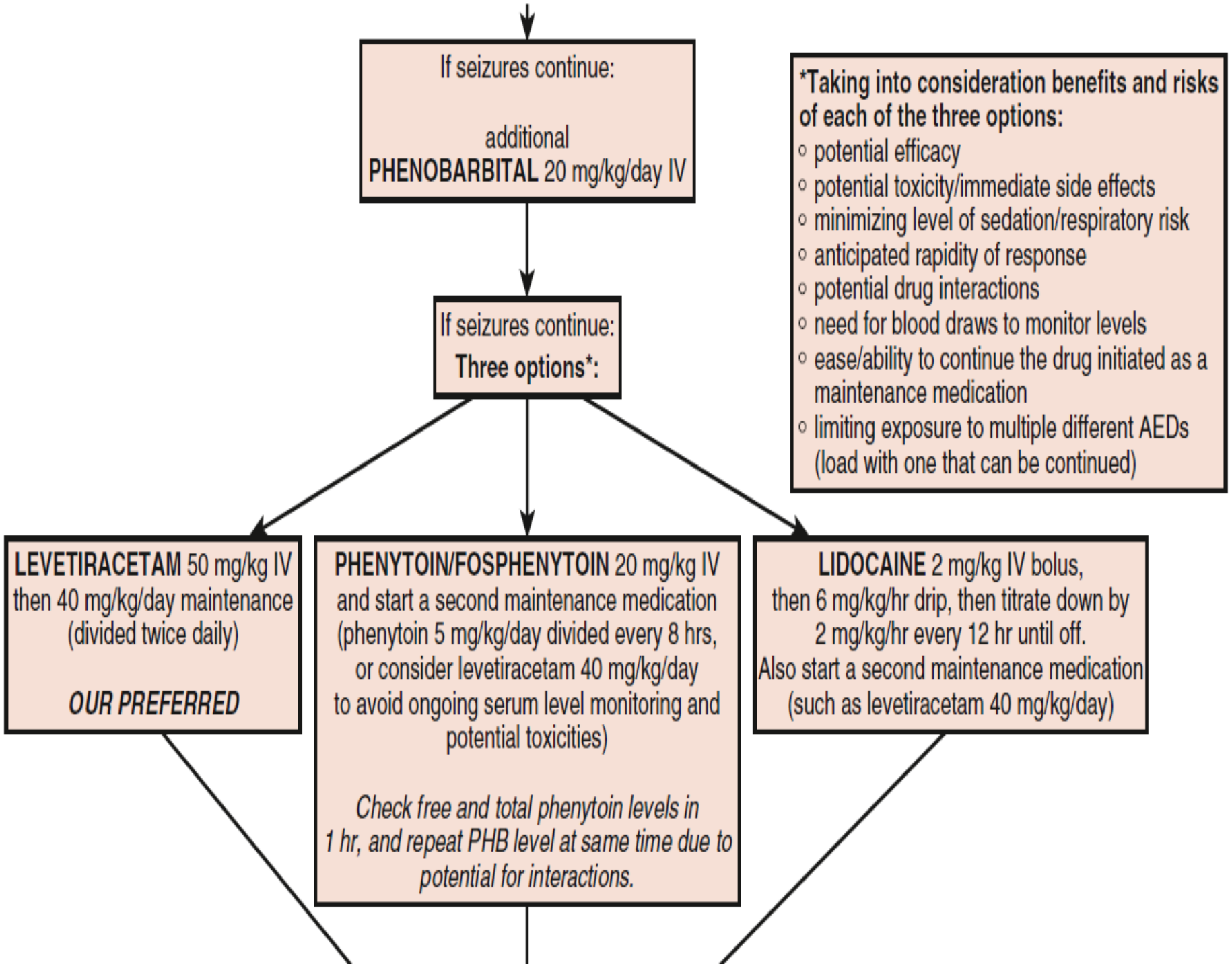
- Clinicians must rely on EEG monitoring as the only means for accurate determination of the adequacy of anticonvulsant therapy.

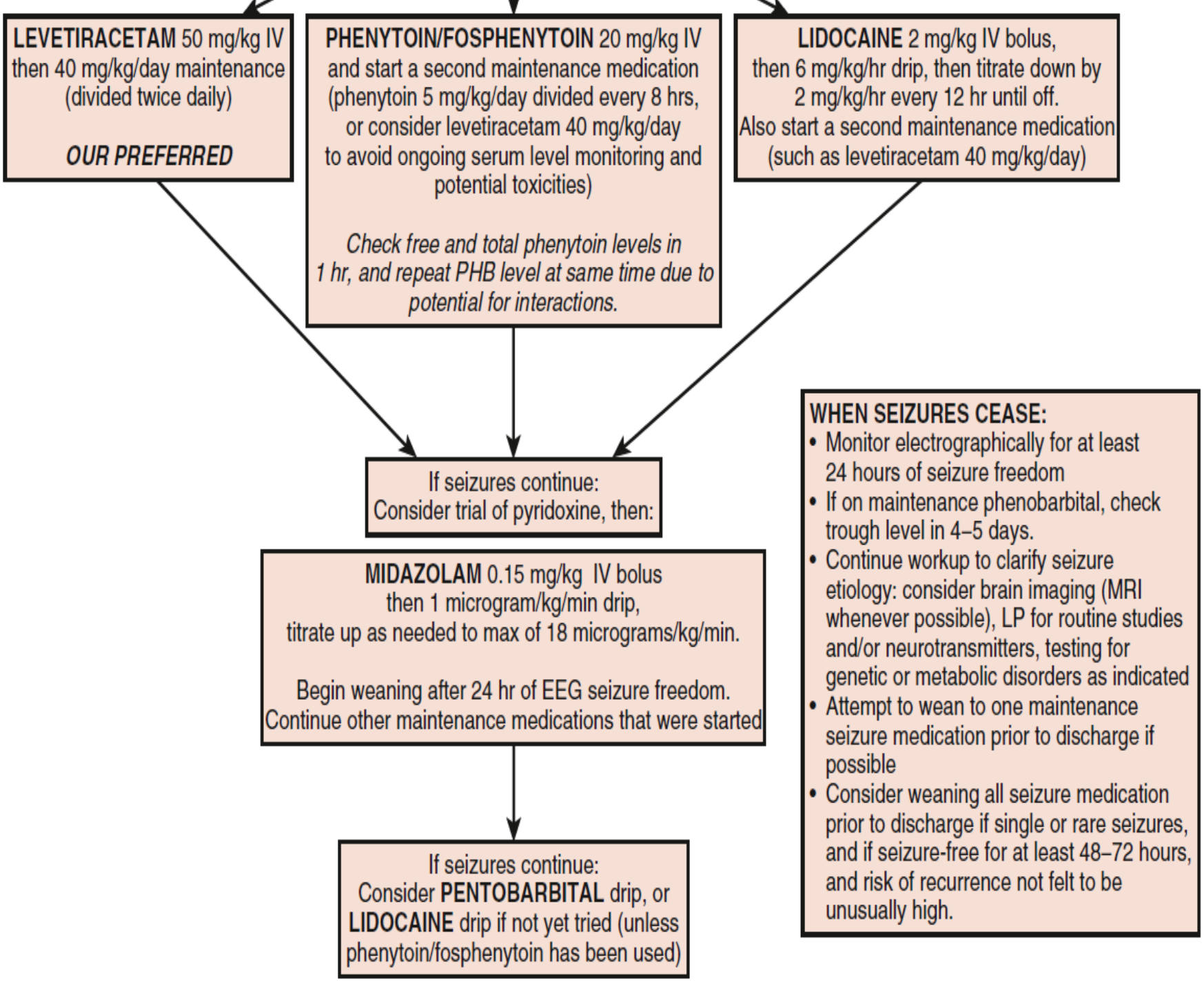
- Although the goal of therapy is generally total or near-total elimination of electrographic seizures, in some newborns the doses of anticonvulsant medications required lead to potentially dangerous disturbances of cardiac function, blood pressure, and ventilation.

- For example, because a newborn with cardiovascular instability may not tolerate multiple anticonvulsant medications, the goal may evolve toward reducing seizure burden as much as possible without worsening cardiovascular function.

- if a diagnosis of brain malformation or other neonatal-onset epileptic encephalopathy is made, the goal might be to reduce seizures as much as possible with an anticonvulsant medication regimen that retains acceptable alertness for long-term use.


Seizures suspected in high-risk neonate:
Confirm seizures with EEG (where available) and start continuous EEG if possible
Check easily correctable causes: glucose, electrolytes
Start antibiotics if febrile or high-risk for CNS infection. LP as soon as seizures stabilized.
If at least one EEG-confirmed seizure and no immediately correctable cause:
PHENOBARBITAL 20 mg/kg IV
and start PHB maintenance 5 mg/kg/day divided BID or Qday
Obtain post-load PHB level in 1–2 hr
Start continuous EEG monitoring if not already done
EEG and clinical response to each medication load should be assessed after 15–20 min


If seizures continue:
additional
PHENOBARBITAL 20 mg/kg/day IV
If seizures continue:
Three options*:
*Taking into consideration benefits and risks of each of the three options:
◦ potential efficacy
◦ potential toxicity/immediate side effects
◦ minimizing level of sedation/respiratory risk
◦ anticipated rapidity of response
◦ potential drug interactions
◦ need for blood draws to monitor levels
◦ ease/ability to continue the drug initiated as a maintenance medication
◦ limiting exposure to multiple different AEDs (load with one that can be continued)
LEVETIRACETAM 50 mg/kg IV then 40 mg/kg/day maintenance (divided twice daily)
OUR PREFERRED
PHENYTOIN/FOSPHENYTOIN 20 mg/kg IV and start a second maintenance medication (phenytoin 5 mg/kg/day divided every 8 hrs, or consider levetiracetam 40 mg/kg/day to avoid ongoing serum level monitoring and potential toxicities)
Check free and total phenytoin levels in 1 hr, and repeat PHB level at same time due to potential for interactions.
LIDOCAINE 2 mg/kg IV bolus, then 6 mg/kg/hr drip, then titrate down by 2 mg/kg/hr every 12 hr until off.
Also start a second maintenance medication (such as levetiracetam 40 mg/kg/day)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OUR PREFERRED
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then 6 mg/kg/hr drip, then titrate down by
2 mg/kg/hr every 12 hr until off.
Also start a second maintenance medication
(such as levetiracetam 40 mg/kg/day)
If seizures continue:
Consider trial of pyridoxine, then:
MIDAZOLAM 0.15 mg/kg IV bolus
then 1 microgram/kg/min drip,
titrate up as needed to max of 18 micrograms/kg/min.
Begin weaning after 24 hr of EEG seizure freedom.
Continue other maintenance medications that were started
If seizures continue:
Consider **PENTOBARBITAL** drip, or
LIDOCAINE drip if not yet tried (unless
phenytoin/fosphenytoin has been used)
WHEN SEIZURES CEASE:
• Monitor electrographically for at least
24 hours of seizure freedom
• If on maintenance phenobarbital, check
trough level in 4–5 days.
• Continue workup to clarify seizure
etiology: consider brain imaging (MRI
whenever possible), LP for routine studies
and/or neurotransmitters, testing for
genetic or metabolic disorders as indicated
• Attempt to wean to one maintenance
seizure medication prior to discharge if
possible
• Consider weaning all seizure medication
prior to discharge if single or rare seizures,
and if seizure-free for at least 48–72 hours,
and risk of recurrence not felt to be
unusually high.

Duration of Therapy

- The optimal duration of anticonvulsant therapy for newborns with seizures relates principally to the likelihood of seizure recurrence if the drugs are discontinued.

- The overall incidence of subsequent epilepsy in neonatal seizure survivors has been reported as between approximately 10% and 30%.

This range can be refined by considering three important, readily identified determinants:

1-neonatal neurologic examination:

(The risk of seizure recurrence is increased to approximately 50% when the neurologic examination at discharge is abnormal)

2-the cause of the neonatal seizures:

(The risk of subsequent epilepsy after seizures secondary to cortical dysgenesis is about 100%. However, simple, late-onset hypocalcemia has essentially no associated risk.)

3-The background EEG pattern.

World Health Organization recommended consideration of weaning of anticonvulsant medication after 72 hours of treatment if the neurologic examination and/or EEG are normal.

- For those infants who require multiple medications for control, each drug should be weaned individually, with phenobarbital being the last to be discontinued.

- Some studies support discontinuing antiseizure medications after resolution of acute symptomatic seizures and prior to hospital discharge.


Thank you
for your
attention