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Proposal of an Algorithm for Diagnosis and Treatment of Neonatal Seizures in Developing Countries

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Summary: Seizures in the neonatal period are common. They can be caused by a variety of conditions, ranging from benign, self-limited illnesses to severe, life-threatening disorders. They are often the first sign of neurologic dysfunction in neonates, and may be used as one factor in considering long-term prognosis. An important mission of the International League Against Epilepsy (ILAE) is to improve the care of patients with epilepsy. Most recently, as part of the Global Campaign against Epilepsy, ILAE, in conjunction with the World Health Organization (WHO), established a new initiative to create clinical guidelines and diagnostic and management algorithms for the care of patients with seizures that can be applied worldwide, including in developing countries with limited or varied medical resources. Created by an international panel of experts in seizure management and guideline development, this document proposes guidelines for the diagnosis and management of the most common and important conditions that cause seizures in the neonatal period. The publication of these clinical pathways for neonatal seizures will be followed by a period of field testing and comment by WHO clinicians and officials before finalization. **Key Words:** Algorithm—Neonatal seizures—Developing countries.

Seizures in the neonatal period are common. They can be caused by a variety of conditions, ranging from benign, self-limited illnesses to severe, prolonged, or life-threatening disorders. They are often the first sign of neurologic dysfunction in neonates and, when present, may be used as one factor in considering long-term prognosis.

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This document proposes guidelines for the diagnosis and management of the most common and important conditions that may cause seizures in the neonatal period. The neonatal period is defined as the day of birth up to 44 weeks' conceptional age. Although this represents a relatively short period, seizure characteristics, pathophysiology, and etiology can be diverse and age dependent. This document suggests etiology-specific therapies for some conditions but does not provide guidelines for the treatment of specific infectious causes of seizures.

These guidelines can be applied at the most-comprehensive clinical care centers. However, it is recognized that clinical care for affected neonates may

be provided where resources and expertise are limited. Thus the guidelines were designed to be applied in a manner dependent on these circumstances. For example, at the most-comprehensive centers, a neonate may undergo extensive diagnostic testing before administration of etiology-specific antiepileptic drug (AED) therapy, whereas at locales with limited resources, care may include only recognition of clinical seizures, initiation of available etiology-specific therapies (even in the absence of confirmatory diagnostic testing), initiation of AED therapy, and, after stabilization, referral to a clinical care center with greater resources, if available. Regardless of resources, the provisions outlined here should guide the clinician through a thorough thought process for management, including history taking, physical examination, causes to consider, an approach to assessment, principles of treatment (including AED management), and prognosis.

These guidelines are not intended as a sole source of guidance in the evaluation of neonates with seizures. Rather, it is intended to assist clinicians by providing a framework for decision making in managing neonatal seizures. It is not intended to replace clinical judgment or to establish a protocol for all neonates with seizures and may not provide the only appropriate approach to this problem. In addition, the guidelines have been developed by epileptologists and neurophysiologists with a specific interest and expertise in neonatal seizures; the approach to this clinical problem by general pediatricians and neonatologists may differ in emphasis.

HISTORY

- Important considerations include
  - Maternal history, including health, prenatal care, and use of medications/drugs
  - Family history of neonatal seizures
  - Pregnancy: Take a detailed history for infections, including **TORCH** infections (**TO**xoplasmosis, **R**ubella, **C**ytomegalovirus, **H**erpes), drug use, medications
  - Labor and delivery: Type and duration of delivery, presence of fetal monitoring, head trauma, need for resuscitation, Apgar scores, venous or arterial blood gas determinations
  - Neonatal history: Birth weight, estimated gestational age at birth (including method of determination), vital signs including body temperature

PHYSICAL EXAMINATION

- Complete a general physical examination that includes assessment of
  - Vital signs
  - Dysmorphic features
  - Evidence of head or other body trauma
  - Skin lesions or discolorations
  - Head circumference
  - Fontanelle fullness: tense or bulging fontanelle suggests meningitis
- Perform a neurologic examination that includes assessment of
  - Level of consciousness
  - Cranial nerves examination
  - Limb movement
  - Muscle tone
  - Primitive and deep tendon reflexes
- Describe abnormal movements suspected of being clinical seizures (Table 1)
  - Note types of movements, including limb and body involvement
  - Note duration and frequency of movements
  - Note whether movements occur during sleep or awake state
  - If the movements are arrested with limb restraint or provoked with tactile stimulation, they are likely to represent normal jitteriness or tremors

TABLE 1. *Description of abnormal movements*

Type	Description
Clonic movements	Rhythmic muscle jerking in one (focal) or more (multifocal or generalized) body parts
Myoclonus	Isolated, or nonrhythmic repetitive muscle jerking in one (focal) or more (multifocal or generalized) body parts
Tonic movements	Extension of all limbs or flexion of arms with extension of legs
Motor automatisms	Mouth: Lip smacking, sucking, or swallowing movements Eyes: Deviations, repetitive blinking, staring Arms and legs: Pedaling, swimming, or stepping movements

TABLE 2. *Characteristics of abnormal movements likely to be correlated with electrographic seizure patterns on electroencephalogram (EEG)*

Description	Examples
Paroxysmal movements with a high correlation with electrographic seizures on EEG	Focal clonic movements Focal tonic movements
Paroxysmal movements that often do NOT correlate with electrographic seizures on EEG, but are associated with encephalopathy	Motor automatisms Myoclonus Bilateral tonic stiffening Multifocal clonic movements
Paroxysmal movements that do not correlate with electrographic seizures on EEG and are not associated with brain pathology	Jitteriness Tremors Sustained myoclonus during sleep

TABLE 3. *Neonatal seizures: causes and prognosis*

Cause	Normal birth	Time of seizure onset	Type of seizure	Prognosis
Hypoxic ischemic encephalopathy	No	<D2	Any	Severe
Infection	Yes	Week 1 to 2	Focal or multifocal	Severe
Stroke	±	D2–D3	Clonic, unilateral	Favorable
Metabolic	Yes	D0	Myoclonic, multifocal	Depends on cause
Pyridoxine deficiency	Yes	D0–M1	Myoclonic, spasms, focal	Favorable if treated early
Brain malformation	±	D0–M1	Spasms, focal	Depends on cause
Benign familial neonatal seizures	Yes	D2–D3	Focal clonic or tonic–clonic,	Favorable
Benign nonfamilial neonatal seizures	Yes	D5	Mostly clonic, often alternating sides	Favorable

D, Day; M, month; ±, normal or abnormal delivery at birth.

- Correlate characteristics of abnormal movements with likelihood of electrographic seizures (Table 2)

CAUSES (Table 3)

- Neonatal encephalopathy
  - **Most common cause of Neonatal seizures**
  - A broad category that suggests brain injury due to acute or chronic asphyxia (i.e., hypoxia, acidosis)
- Infections
  - Conditions to consider include
    - Sepsis
    - Meningitis

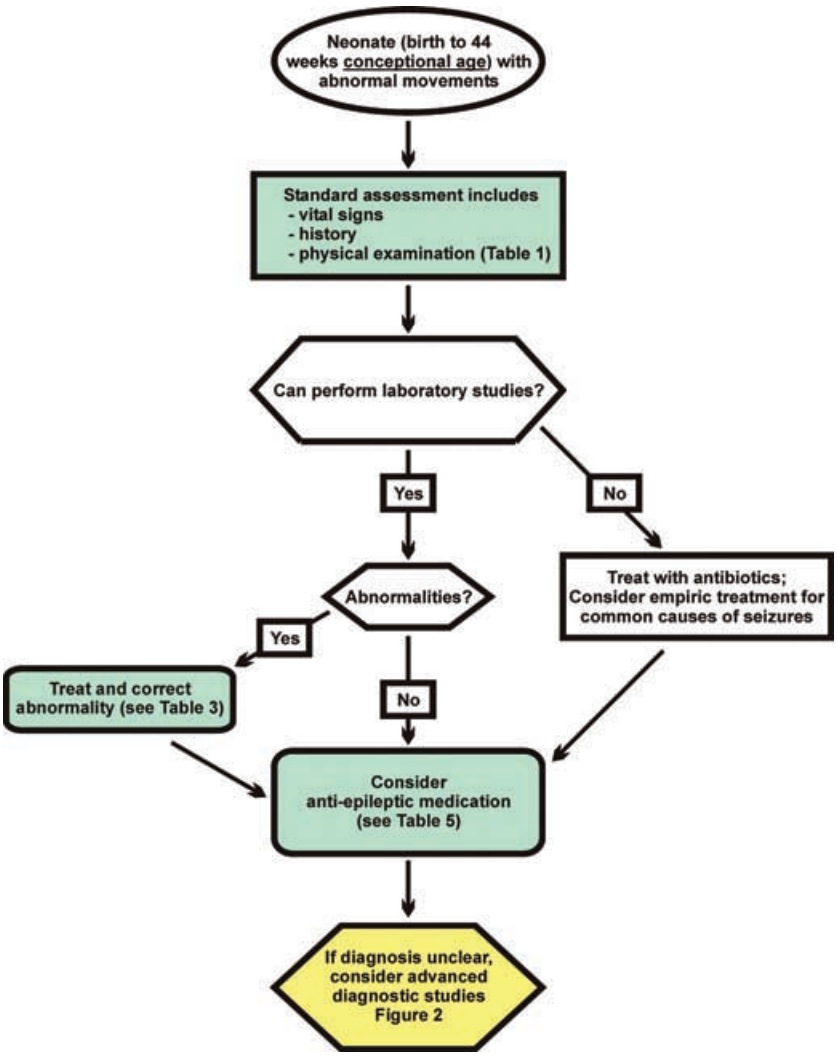

FIG. 1. Initial management of abnormal movements

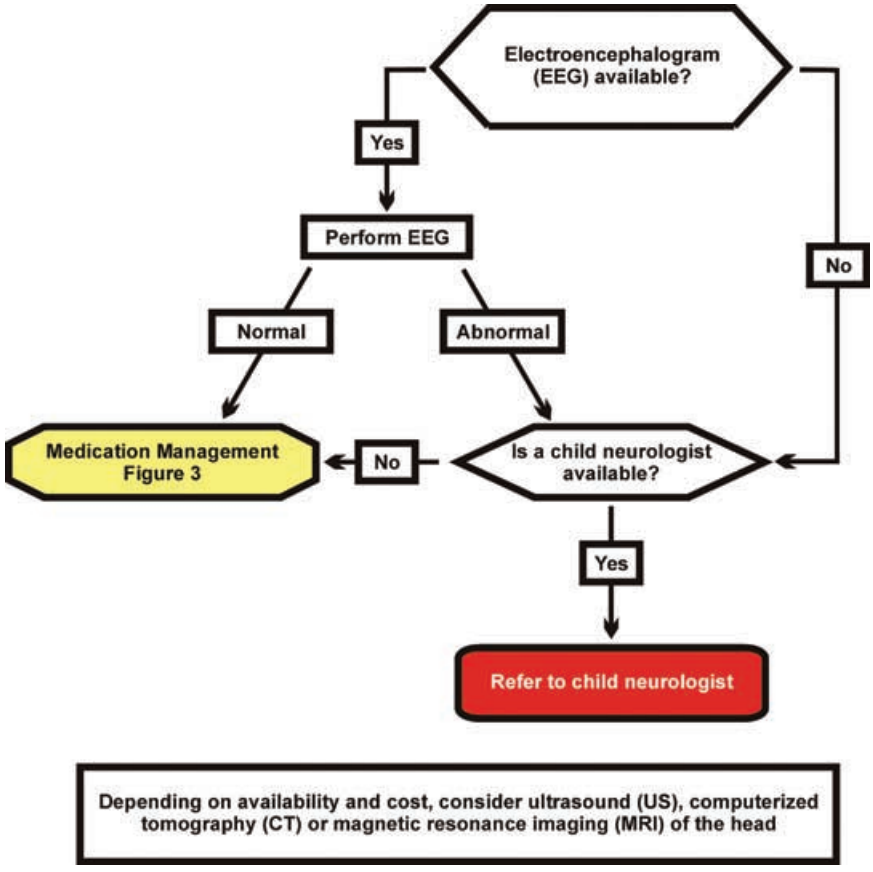

FIG. 2. Advanced diagnostic studies.

- Encephalitis [particularly herpes simplex virus (HSV)]
- Organisms to consider include
  - Bacteria: Streptococcus agalactiae (group B streptococcus), Enterococcus (group D streptococcus), Escherichia coli, Neisseria gonorrhoeae, Listeria monocytogenes, Chlamydia trachomatis
  - TORCH infections [toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus (HSV)]
  - Treponema pallidum (syphilis)
  - Human immunodeficiency virus (HIV)

- Metabolic
  - Hypoglycemia (often associated with asphyxia, low birth weight, growth retardation, maternal diabetes, infection, cold stress)
  - Hypocalcemia
  - Hypomagnesemia
  - Hyponatremia
  - Hypernatremia
  - Inborn errors of metabolism
  - Pyridoxine-dependent seizures (rare)
- Vascular
  - Stroke
  - Intracranial hemorrhage: more common in infants younger than 32 weeks' gestation
    - Premature infants: Periventricular–intraventricular hemorrhage most likely
    - Term infants: Subarachnoid or subdural hemorrhage most likely
- Brain malformations
- Trauma
- Maternal drug use
- Benign disorders
  - Benign familial neonatal seizures
  - Benign neonatal seizures
- Cryptogenic
  - In some seizures disorders, an etiology cannot be identified

APPROACH TO ASSESSMENT (Figs. 1 and 2)

- Assessment for causes should be guided by a number of principles
  - Consider common causes
  - Consider treatable causes
  - After initial screening evaluation, individualize the assessment
- Diagnostic studies to consider
  - Complete blood count
  - Glucose
  - Calcium
  - Magnesium

TABLE 4. *Treatment of metabolic causes of neonatal seizures*

	Immediate therapy	Maintenance therapy
Glucose, 10% solution	2 ml/kg IV	Up to 8 mg/kg/min IV
Calcium gluconate 10% solution (9.4 mg of elemental Ca/ml)	2 ml/kg IV over 10-min period (18 mg of elemental Ca/kg)	8 mg/kg/day IV (75 mg of elemental Ca/kg/day)
Magnesium sulfate 50% solution (50 mg of elemental Mg/ml)	0.25 ml/kg IM	0.25 ml/kg IM repeated every 12 hours until magnesium normal
Hypertonic saline, 3% solution (0.5 mEq/ml). To be used only in severe hyponatremia resulting in severe symptoms such as seizures, altered mental status, or signs of brainstem herniation	1 ml/kg will raise the plasma sodium by ~1 mEq/L. The goal is to arrest seizures by correcting the sodium ~4–6 mEq/L over the first 1- to 2-h period, with an eventual goal of a serum sodium of 125–130 mEq/L	Determine the etiology of the hyponatremia with careful fluid management. Correction of the sodium too rapidly, particularly in cases of chronic hypernatremia, can result in osmotic demyelination syndrome
Pyridoxine	100 mg IV	

- Sodium
- Lumbar puncture
- Toxicology screen (maternal serum or urine; infant serum, urine or meconium)
- In a malarious area, prepare a blood smear
- Advanced diagnostic studies: consider depending on cost/availability (Fig. 2)
  - Electroencephalogram (EEG)
  - Neuroimaging: Ultrasound, computerized tomography (CT), or magnetic resonance imaging (MRI) of the head

- Initial assessment to consider causes, including
  - Neonatal encephalopathy (history, examination, laboratory evaluation)
    - Need for resuscitation in the delivery room
    - Presence of depressed level of consciousness
    - Evidence of multi–organ system involvement
  - Infections: (examination and laboratory evaluation)
    - Meningitis: Lethargy, a tense/bulging fontanelle, apneic episodes, or high-pitched cry is suggestive
    - Encephalitis
    - Intrauterine/maternal infections
    - Sepsis
  - Metabolic disturbances: (laboratory evaluation)
    - Hypoglycemia
    - Hypocalcemia
    - Hypomagnesemia
    - Hyponatremia
    - Hypernatremia
  - Vascular/brain abnormalities/trauma (neuroimaging)
  - Maternal drug use (history, laboratory evaluation)
    - Toxicology screen: maternal
    - Toxicology screen: infant

PRINCIPLES OF TREATMENT

Neonates who are experiencing ongoing clinical seizures require immediate treatment, with initial attention to maintaining airway, breathing, and circulation. This is particularly applicable for abnormal movements previously shown to have a high correlation with electrographic seizures on EEG (Table 2). At times, treatment is initiated for abnormal movements that have been shown often not to correlate with electrographic seizures on EEG but are associated with an encephalopathy. If resources to conduct a thorough evaluation for etiology are not available, etiology-specific therapies for common treatable causes may be instituted. Treatment for the metabolic disturbances, bacterial meningitis, and viral encephalitis should be initiated and not be delayed before performing diagnostic testing such as lumbar puncture and serum analysis

TABLE 5. *Antiepileptic medications for the treatment of neonatal seizures*

Drug	Dose		Average therapeutic range	Apparent half-life
	Loading	Maintenance		
Phenobarbital (1st choice)	20 mg/kg IV/IM (≤40 mg/kg)	3–5 mg/kg/24 h divided every 12 h IV, IM, PO	20–40 μg/L	100 h after day 5–7
Phenytoin (2nd choice, use if phenobarbital not available or not successful)	15 to 20 mg/kg IV (over 30- to 45-min period)	3–8 mg/kg/24 h divided every 8 to 12 h IV/PO	10–20 μg/L	100 h (40–200)
Diazepam	0.25 mg/kg IV (bolus) 0.5 mg/kg (rectal)	May be repeated 1 to 2 times	No test available	31–54 h
Lorazepam	0.05 to 0.1 mg/kg (IV) (over 2- to 5-min period)	May be repeated	No test available	31–54 h

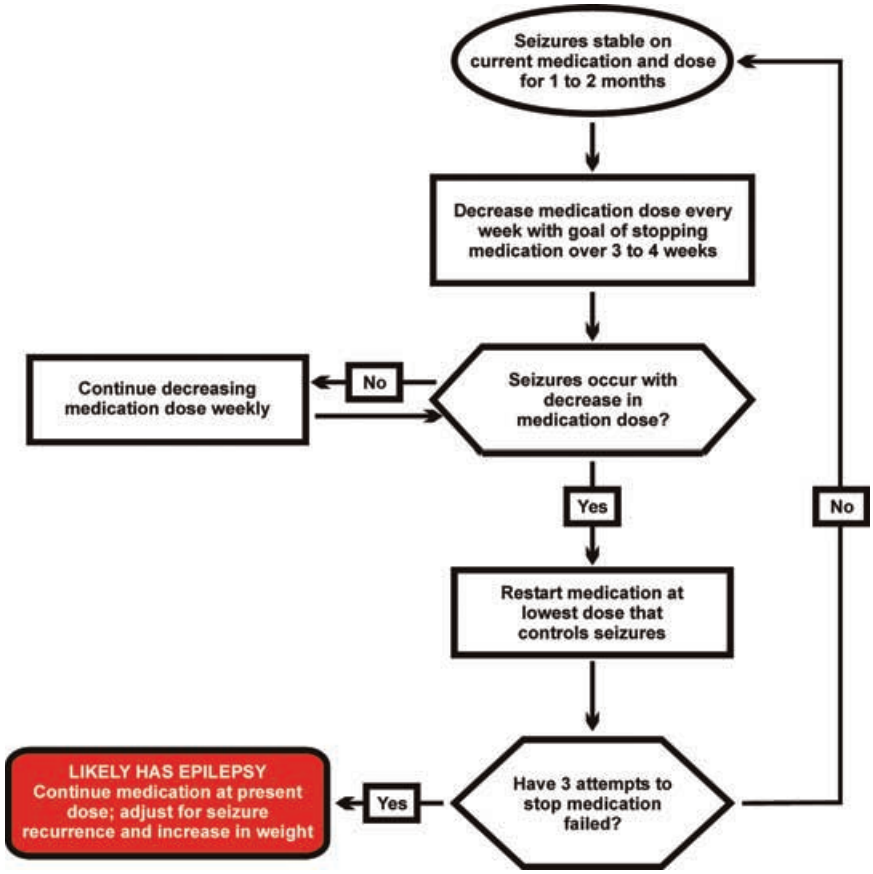

FIG. 3. Medication management

- Etiology-specific treatment of metabolic causes: Table 4
- Antiepileptic (AED) drug therapy: Table 5
- If seizures of unknown cause persist despite use of an AED, consider a trial of pyridoxine: Table 4

ANTIEPILEPTIC DRUG (AED) MANAGEMENT (Fig. 3)

AED management is based on pathophysiology of the clinical seizures, seizure duration, and seizure frequency.

- Begin AED therapy with a first-line drug (Table 5), titrating to maximal tolerated dosages to control clinical seizures (if EEG is not available) or electrical seizures if EEG is available
- Initiate second-line AED if first-line AED fails
- Limited consensus exists concerning the duration of long-term AED therapy and controlling seizures. However, after medication is initiated and the seizures are controlled, AEDs can be discontinued gradually, decreasing medication dose weekly
  - If the infant is taking medication and seizures recur, increase the dose back to levels at which no seizures occurred, and then attempt to discontinue medications in 1 to 2 months
- If repeated attempts to discontinue medications have been made with no success, the child may have epilepsy: attempt referral to a neurologist

PROGNOSIS (Table 3)

- Prognosis is most closely tied to underlying etiology of seizures. Etiologic factors that cause diffuse brain injury are associated with relatively poor long-term outcome, whereas those more closely associated with focal brain injury and relatively sparing of greater regions of the brain suggest a more favorable outcome. Seizure types associated with diffuse brain injury include
  - Generalized myoclonic seizures
  - Generalized tonic seizures
  - Motor automatisms (traditionally referred to as subtle seizures), although such movements have a poor correlation with electrographic seizures on EEG
- Other factors associated with poor outcome include
  - Severe abnormalities on neurologic examination
  - Prematurity
  - Early onset (within 48 h after birth)
  - Repeated seizures of duration leading to status epilepticus, defined as repeated seizures of $\geq$1 h
  - Recurrent seizures for a period of $>$48 h

- Factors associated with a favorable outcome include
  - Normal neurologic examination, including normal level of alertness at the time of seizure onset
  - Brief or rarely recurring seizures
  - Focal clonic seizures: Often associated with relatively benign conditions such as
    - Benign familial neonatal seizures
    - Benign idiopathic neonatal seizures
    - Metabolic abnormalities (hypocalcemia)
    - Focal lesions (brain hemorrhage or stroke)
    - Lesions confined to relatively circumscribed brain regions

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