

# STATUS UPDATES ON NEONATAL SEIZURES AND STATUS EPILEPTICUS

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## Disclosures

- I consult for Wolters Kluwer Clinical Drug Information, Inc. for Lexi-drug<sup>TM</sup> as a member of the Neonatal Advisory Panel.
- I will be discussing off-label use of medications.

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## LEARNING OBJECTIVES

- Describe the unique pathophysiology and risk factors for neonatal seizures
- Analyze literature comparing first-line agents for the management of neonatal seizures
- Evaluate novel agents for refractory neonatal seizures
- Review vitamin-responsive metabolic causes of neonatal seizures
- Develop a treatment algorithm for the management of neonatal seizures

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## BACKGROUND

- Epidemiology:
  - Seizures = most common neurologic emergency in neonates
  - Incidence: 1-5 per 1000 live births
    - Increased in preterm neonates
- Long-term sequelae: cognitive deficits, epilepsy, mortality

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## PATHOPHYSIOLOGY

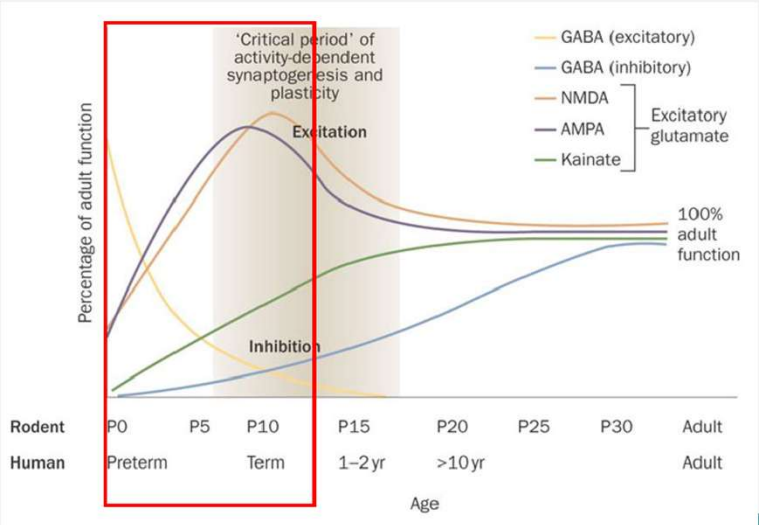
- Hyperexcitable state
- Neurotransmitter receptors have developmental differences
  - ↑ Expression of glutamate receptors (NMDA,AMPA)
  - ↓ Binding and expression of GABA receptors

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## PATHOPHYSIOLOGY



Percentage of adult function

Age

Rodent: P0, P5, P10, P15, P20, P25, P30, Adult

Human: Preterm, Term, 1-2yr, >10yr, Adult

Legend:

- GABA (excitatory)
- GABA (inhibitory)
- NMDA
- AMPA
- Kainate

Excitatory glutamate


Inhibition

100% adult function

'Critical period' of activity-dependent synaptogenesis and plasticity

Jensen, et al. *Clin Perinatol*. 2009.

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## PATHOPHYSIOLOGY

- GABA = net excitatory effects in immature neurons
  - ↑ relative intracellular chloride concentration
- GABA subunit composition of receptors is different

Peerboom, et al. *Neurosci Biobehav Rev.* 2021.

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## ETIOLOGY

- Perinatal asphyxia/HIE**
- Metabolic abnormalities
- Intracranial hemorrhage
- Stroke
- Encephalitis or meningitis
- Congenital brain malformations
- Genetic disorders

*Causes of Acute Reactive Seizures in Term Neonates.*

Pressler, et al. *Epilepsia.* 2023.  
Yozowitz E, et al. *N Eng J Med.* 2023.

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## CLINICAL MANIFESTATIONS

- Often more subtle than older children
  - Lip smacking
  - Bicycling
  - Eye deviation
  - Head turning
  - Jittery movements

- 5 major categories:



Pressler, et al.  
*Epilepsia*. 2023.

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## DIAGNOSIS

- Gold Standard = Electroencephalogram (EEG)
  - Discharges > 10 seconds typically = seizure
- Clinical seizures
  - Based on clinical manifestations alone
  - Limitation: may not be true seizures if EEG not evaluated
- Imaging: MRI or CT
  - Used to identify potential causes of seizures (e.g., structural abnormalities, hemorrhages)

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## HISTORY OF ANTIEPILEPTIC DRUGS

Level	Definition	Course of Action
Level 1: Definite seizure	Suspected seizure with a continuous EEG correlate	Treat
Level 2: Probable seizure	Suspected seizure with an amplitude-integrated EEG correlate or clinically assessed focal clonic or tonic seizure	Treat
Level 3: Possible seizure	Clinical seizure other than focal tonic or clonic	Consider treatment
Level 4: Suspected seizure	Insufficient evidence to meet seizure criteria	Do not treat
Level 5: Not a seizure	Movement determined by EEG not to be a seizure	Do not treat

\* Seizures defined as definite or probable should be managed with antiseizure medication. If electroencephalography (EEG) is not available, the clinician can rely on levels 3, 4, and 5, deciding whether an event is a seizure solely on the basis of clinical semiology. The levels of diagnostic certainty were proposed by the Brighton Collaboration.

Yozowitz E, et al. *N Eng J Med*. 2023.

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## HISTORY OF ANTIEPILEPTIC DRUGS

- Diagnostic work-up should include:

Urgent Evaluation	Suspected HIE	Suspected Infection	Suspected Stroke	Suspected Metabolic Disorder
Obtain immediate laboratory measurements, including glucose, electrolytes, and full blood count; confirm with EEG or amplitude-integrated EEG	Check birth history and Apgar score; screen for other causes, depending on clinical scenario; assess need for therapeutic hypothermia	Obtain blood cultures and TORCH titers; CSF studies: glucose and protein, cell counts, PCR assay for HSV, culture; pathological assessment of placenta	Imaging: MRI with diffusion-weighted imaging; evaluate for cause (e.g., thrombophilia or vascular or cardiac cause); echocardiogram; pathological assessment of placenta	Screen for other metabolic abnormalities (screen includes amino acids, ammonia, lactate, pyruvate, very-long-chain fatty acids, urine, organic acids, biotinidase, pipecolic acid, pyridoxine, pyridoxal-5-phosphate); ophthalmologic evaluation

\* CSF denotes cerebrospinal fluid, HIE hypoxic ischemic encephalopathy, HSV herpes simplex virus, PCR polymerase chain reaction, MRI magnetic resonance imaging, and TORCH toxoplasmosis, other (syphilis, varicella, mumps, parvovirus, human immunodeficiency virus, and Zika), rubella, cytomegalovirus, and HSV.

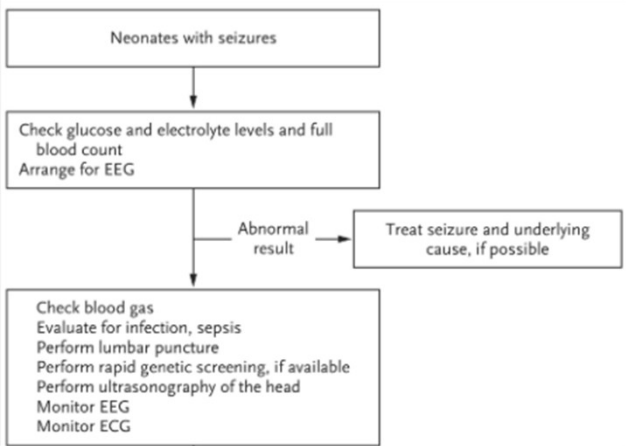
Yozowitz E, et al. *N Eng J Med*. 2023.

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## HISTORY OF ANTIEPILEPTIC DRUGS



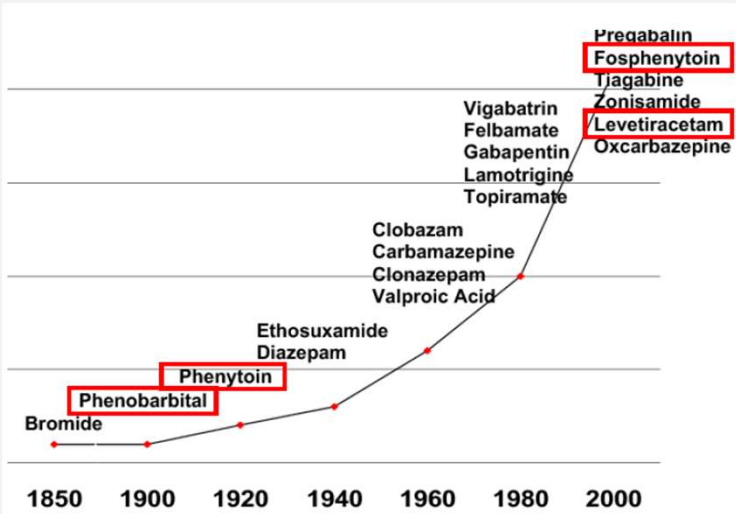
Yozowitz E, et al. *N Eng J Med*. 2023.



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## HISTORY OF ANTIEPILEPTIC DRUGS



Pressler, et al. *Epilepsia*. 2023.



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# FIRST-LINE MANAGEMENT

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## FIRST-LINE MANAGEMENT

- Phenobarbital

Mechanism	Acts on GABA receptors to open chloride channels; inhibits AMPA glutamate receptor
Dosing	Load: 15-20 mg/kg (may repeat up to 40 mg/kg total) Maintenance: 3-5 mg/kg/day divided BID
PK	Linear PK – anticipate dose of 20 mg/kg to achieve a level of 20 mcg/mL (volume of distribution in neonates ~1 L/kg)
TDM	Goal serum concentration 15-40 mcg/mL
Adverse Effects	Hypotension, bradycardia, respiratory depression Concern for neuronal apoptosis and long-term cognitive impairment
Drug Interactions	CYP3A4 inducer

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## FIRST-LINE MANAGEMENT

- Phenytoin/Fosphenytoin

Mechanism	Inhibits voltage-gated sodium channels
Dosing	Load: 15-20 mgPE/kg Maintenance: 4-8 mgPE/kg/day divided BID
PK	Highly protein bound <ul style="list-style-type: none"> <li>Neonates have less plasma proteins</li> </ul>
TDM	Goal: 8-15 mcg/mL (total), 1-2 mcg/mL (free) <ul style="list-style-type: none"> <li>Lower total PHT goal than older children/adults</li> <li>Free PHT level may be more reliable</li> </ul>
Adverse Effects	Hypotension, cardiac arrhythmias <ul style="list-style-type: none"> <li>Max rate 2 mgPE/kg/min (up to 150 mgPE/min)</li> </ul> Hepatotoxicity, "purple glove syndrome", dermatologic reactions
Drug Interactions	CYP3A4 inducer

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## FIRST-LINE MANAGEMENT

- Phenobarbital Compared with Phenytoin for the Treatment of Neonatal Seizures (1999)

Study Design	Single-blinded, randomized study
Patient Population	59 neonates at risk for seizures due to abnormal movements, low Apgar scores, traumatic delivery, CNS infections or malformations
Intervention	All infants underwent EEG monitoring Randomized to phenobarbital (n=30) or phenytoin (n=29) at doses to achieve plasma concentrations of free drug of 25 mcg/mL and 3 mcg/mL, respectively
Primary Outcome	Complete control of EEG-confirmed seizures in 43% of PB patients and 45% of PHT patient (p=1.0)
Secondary Outcomes	<ul style="list-style-type: none"> <li>The severity of initial seizure activity was inversely related to the successful control of seizures in both groups</li> <li>No significant changes in heart rate, rhythm, MAP or respiratory status were reported in either group</li> </ul>

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Painter, et al. N Engl J Med . 1999.



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## FIRST-LINE MANAGEMENT

- Phenobarbital Compared with Phenytoin for the Treatment of Neonatal Seizures (1999)

Limitations	Did not include preterm neonates who are often at higher risk for neonatal seizures Concentration of PB in the study was moderately therapeutic compared to supratherapeutic levels of PHT <ul style="list-style-type: none"><li>Plasma concentrations of 25 mcg/mL (PB) and 3 mcg/mL (free PHT)</li></ul>
Conclusion	If additional loading doses of PB were given to reach the levels of 40-50 mcg/mL required for some neonates to abort seizures, <u>PB would likely have been superior to PHT</u>

Painter, et al. N Engl J Med . 1999.

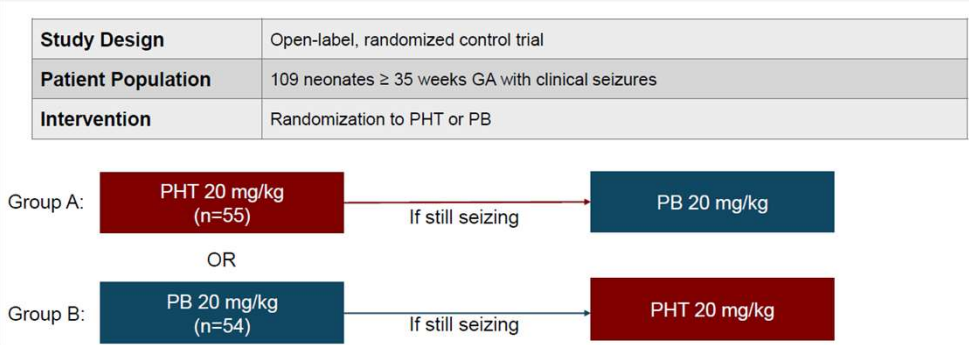


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## FIRST-LINE MANAGEMENT

- Phenobarbitone Versus Phenytoin for Treatment of Neonatal Seizures : An Open Label Randomized Control Trial (2013)



Pathak, et al. Indian Pediatr . 2013.



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## FIRST-LINE MANAGEMENT

- Phenobarbitone Versus Phenytoin for Treatment of Neonatal Seizures : An Open Label Randomized Control Trial (2013)

Primary Outcome	Cessation of clinical seizure activity <ul style="list-style-type: none"><li>After initial 20 mg/kg loading dose: 72.2% in PB group vs 14.5% in PHT group (p&lt;0.001)</li><li>After crossover to the opposite drug: 96.3% in PB group vs 80% in PHT group (p&lt;0.05)</li></ul>
Secondary Outcomes	No differences between PB and PHT in survival at discharge, time to control seizure, or significant adverse effects
Limitations	Limited EEG monitoring available during treatment Did not include preterm neonates
Conclusion	<ul style="list-style-type: none"><li>PB is more efficacious than PHT in control of clinical seizures</li><li>In neonates who received PHT as first line, after crossing over to receive PB the cessation of seizures increased by 65.5%</li><li>Doses &gt; 20 mg/kg of PB may be required to improve response</li></ul>

Pathak, et al. Indian Pediatr . 2013.

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## FIRST-LINE MANAGEMENT

- Levetiracetam

Mechanism	Regulates the release of neurotransmitters
Dosing	Load: 40-60 mg/kg Maintenance: 20-60 mg/kg/day divided BID
PK	Clearance is decreased in patients with renal dysfunction
TDM	Not routinely done
Adverse Effects	Minimal to none <ul style="list-style-type: none"><li>May have beneficial effects on neurologic outcomes</li></ul>
Drug Interactions	Minimal to none

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## FIRST-LINE MANAGEMENT

- Role of Intravenous Levetiracetam for Acute Seizure Management in Preterm Neonates (2013)
  - Retrospective (n=12)

**TABLE.**  
Seizure management in preterm neonates

Patients	EGA/Sex	Birth Weight (kg)	Apgar 1 min/5 min	Etiology of SZ	Indication for LEV Use	Route	Loading Dose (mg/kg)	Response to LEV at 24 h	Adverse Events
1	33.4/F	2.258	5/8	HSV meningoencephalitis	Initially LD with LEV	IV	50	Yes	None
2	24.2/M	0.62	4/7	Unknown	Continued SZ on PB	IV	25	Yes	None
3	34.2/F	2.067	9/9	Hemorrhage	Initially LD with LEV	IV	50	Yes	None
4	34/F	2.42	1/3	HIE	Continued SZ on PB	IV	50	Yes	None
5	31/M	2.051	1/1	Hemorrhage	Continued SZ on PB	IV	50	No	None
6	35/M	2.081	5/7	Unknown	Initially LD with LEV	IV	50	Yes	None
7	34.3/F	2.554	2/6	Hemorrhage	Continued SZ on PB	IV	50	Yes	None
8	36/M	2.21	0/0	HIE	Continued SZ on PB	IV	50	No	None
9	35.2/F	2.96	0/4	HIE	Continued SZ on PB	IV	25	Yes	None
10	23.3/M	0.65	5/6	Unknown	Continued SZ on PB	IV	25	Yes	None
11	36/F	1.9	1/4	HIE	Switch from PB	IV	25	N/A	None
12	32.1/F	2.03	0/1	HIE	Continued SZ on PB	IV	25	Yes	None

Khan et al. Pediatr Neurol. 2013

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## FIRST-LINE MANAGEMENT

- Adverse Neurodevelopmental Outcomes After Exposure to Phenobarbital and Levetiracetam for the Treatment of Neonatal Seizures (2013)
  - Retrospective, single-center
  - Phenobarbital (n=247) vs levetiracetam (n=174)
    - NOTE: some neonates received both (n=141)
  - Cumulative doses through hospital discharge:
    - Phenobarbital 60 mg/kg
    - Levetiracetam 360 mg/kg

Maitre, et al. J Perinatol . 2013

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## FIRST-LINE MANAGEMENT

- Adverse Neurodevelopmental Outcomes After Exposure to Phenobarbital and Levetiracetam for the Treatment of Neonatal Seizures (2013)
  - Neurodevelopmental outcomes at 2 years of age:
    - Phenobarbital: scores ↓ by 8-9 pts for every 100 mg/kg exposure
    - Levetiracetam: scores ↓ by 2.2-2.6 pts for every 300 mg/kg exposure

Maitre, et al. J Perinatol . 2013

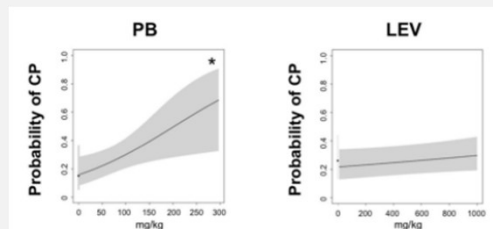


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## FIRST-LINE MANAGEMENT

- Adverse Neurodevelopmental Outcomes After Exposure to Phenobarbital and Levetiracetam for the Treatment of Neonatal Seizures (2013)
  - Diagnosis of cerebral palsy at 2 years of age:
    - Phenobarbital ↑ 2.3x for every 100 mg/kg exposure (p=0.018)
    - No association for levetiracetam



Maitre, et al. J Perinatol . 2013

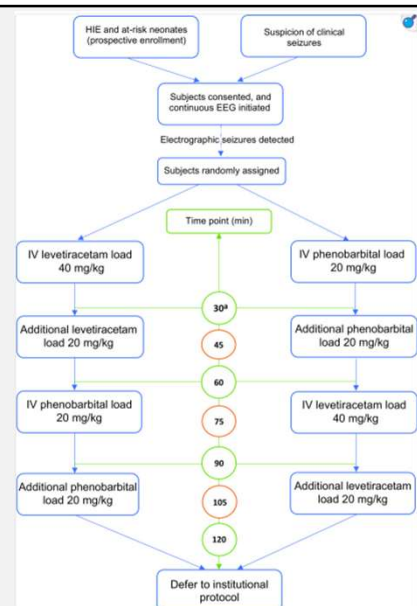


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## FIRST-LINE MANAGEMENT

- Levetiracetam versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial (2020)
  - Multi-center, blinded, RCT
  - Term infants  $\geq 2.2$  kg
  - At risk for or suspected seizures
  - Randomized 60:40 (n=83)
  - Outcome: EEG-confirmed seizures



Sharpe, et al. Pediatrics 2020.



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## FIRST-LINE MANAGEMENT

- Levetiracetam versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial (2020)

TABLE 2 Prespecified Primary and Secondary Outcome Measures (Modified Intention-To-Treat Population)

	Phenobarbital (20–40 mg/kg), n (Cessation %)	Levetiracetam (40–60 mg/kg), n (Cessation %)	Fisher's Exact P	Relative Risk (95% CI)
Primary outcome measure				
24-h seizure cessation rate (N = 83)	24 of 30 (80)	15 of 53 (28)	<0.001	0.35 (0.22–0.56)
Secondary outcome measures				
48-h Seizure cessation rate (N = 75)	18 of 28 (64)	8 of 47 (17)	<0.001	0.26 (0.13–0.53)
1-h Seizure cessation rate (N = 83)	28 of 30 (93)	26 of 53 (49)	<0.001	0.53 (0.39–0.7)
Subanalysis of patients with HIE treated with hypothermia				
24-h seizure cessation rate (N = 27)	9 of 10 (90)	6 of 17 (35)	0.014	0.39 (0.2–0.77)

- More hypotension with phenobarbital (17% vs 5%, p=0.05)
- Limitations:
  - Small sample size (did not meet power)
  - No preterm neonates

Sharpe, et al. Pediatrics 2020.




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## FIRST-LINE MANAGEMENT

- Efficacy and Safety of Levetiracetam vs. Phenobarbital for Neonatal Seizures:A Systematic Review and Meta-Analysis (2021)
  - Phenobarbital vs levetiracetam as first-line for neonatal seizures
  - Meta-analysis including 10 studies (n=930 neonates)
    - 4 retrospective
    - 2 prospective cohort
    - 4 randomized controlled trials
  - Dosing variable among studies:
    - Phenobarbital 10-40 mg/kg
    - Levetiracetam 20-60 mg/kg

Qiao, et al. Front Neurol. 2021.

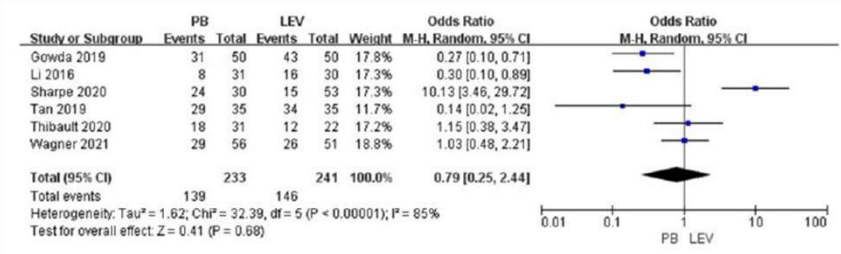


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## FIRST-LINE MANAGEMENT

- Efficacy and Safety of Levetiracetam vs. Phenobarbital for Neonatal Seizures:A Systematic Review and Meta-Analysis (2021)
  - Clinical seizures: levetiracetam > phenobarbital (OR 0.24, CI 0.1-0.58; p=0.002)
  - EEG-confirmed seizures: no difference (OR 1.53, CI 0.2-11.5; p=0.68)**




Study or Subgroup	PB		LEV		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Gowda 2019	31	50	43	50	17.8%	0.27 [0.10, 0.71]
Li 2016	8	31	16	30	17.3%	0.30 [0.10, 0.89]
Sharpe 2020	24	30	15	53	17.3%	10.13 [3.46, 29.72]
Tan 2019	29	35	34	35	11.7%	0.14 [0.02, 1.25]
Thibault 2020	18	31	12	22	17.2%	1.15 [0.38, 3.47]
Wagner 2021	29	56	26	51	18.8%	1.03 [0.48, 2.21]
<b>Total (95% CI)</b>		<b>233</b>		<b>241</b>	<b>100.0%</b>	<b>0.79 [0.25, 2.44]</b>
Total events	139		146			

Heterogeneity: Tau<sup>2</sup> = 1.62; Chi<sup>2</sup> = 32.39, df = 5 (P < 0.00001); I<sup>2</sup> = 85%  
Test for overall effect: Z = 0.41 (P = 0.68)

FIGURE 3 | Comparison of efficacy in the PB and LEV groups. M-H, Mantel-Haenszel; CI, confidence interval.

Qiao, et al. Front Neurol. 2021.



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FIRST-LINE MANAGEMENT

- Efficacy and Safety of Levetiracetam vs. Phenobarbital for Neonatal Seizures:A Systematic Review and Meta-Analysis (2021)
  - Adverse events: phenobarbital was worse (hypotension, respiratory depression)

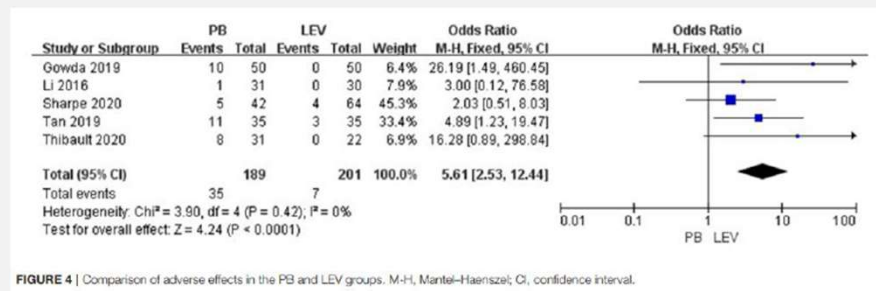


FIGURE 4 | Comparison of adverse effects in the PB and LEV groups. M-H, Mantel-Haenszel; CI, confidence interval.

Qiao, et al. Front Neurol. 2021.



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FIRST-LINE MANAGEMENT


Study	Methods	Outcomes	Conclusion
Thibault (2020)	Retrospective, single-center N=53 post-op cardiac surgery PB 20 mg/kg vs. LEV 30 mg/kg	Complete control of seizures on EEG in 58% PB and 55% LEV (p=1.0)	No significant difference in efficacy between PB and LEV
Verwoerd (2022)	Retrospective cohort study N=25 PB 20 mg/kg vs. LEV 50 mg/kg	Sustained seizure burden on EEG < 10% in 65% LEV and 63% PB Seizure freedom on EEG in 35% LEV and 25% PB	No difference in sustained low seizure burden or seizure freedom between PB and LEV
Akeel (2022)	Prospective, double-blind RCT N=104 PB 20 mg/kg vs. LEV 20 mg/kg +/-additional 10 mg/kg if needed	Clinical seizure cessation maintained for 24 hours in 65.4% PB and 78.8% LEV (p=0.01) No adverse events in LEV group vs. 12 events in PB group No EEG was performed	LEV was found to have better efficacy and safety compared to PB as first line (but no EEG assessment)

Thibault, et al. Epilepsia . 2020  
Verwoerd, et al. J Child Neurol. 2022  
Akeel, et al. Glob Pediatr Health. 2022




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FIRST-LINE MANAGEMENT			
Study	Methods	Outcomes	Conclusion
Susnerwala (2022)	Open-label, single-center, RCT N=82 asphyxiated neonates PB 20 mg/kg vs. LEV 20 mg/kg	Clinical seizure control maintained for 24 hours in 34.2% PB and 65.9% LEV (p<0.05, RR 0.52, CI 0.32-0.84)	LEV was more effective than PB for seizures in asphyxiated infants (no EEG assessment)
Gyandeep (2023)	Open-label, parallel RCT N=48 preterm neonates PB 15 mg/kg vs LEV 40 mg/kg	Cessation of clinical seizures maintained for 24 hours in 70% PB and 79% LEV (p=0.504)	Comparable efficacy of PB and LEV in preterm neonates (no EEG assessment)
Bättig (2023)	Retrospective cohort study N=108 preterm and term neonates PB 15-20 mg/kg vs LEV 30 mg/kg	Complete response on EEG in 36% PB and 45% LEV (p=0.4) Partial response on EEG in 64% PB and 55% LEV Adverse effects in 24% PB and 1% LEV (hypotension, respiratory depression) (p<0.001)	Efficacy was similar between PB and LEV Significantly more adverse events in the PB group than LEV group
<div>Susnerwala, et al. Hosp Pediatr. 2022 Gyandeep, et al. Eur J Pediatr 2023 Bättig, et al. Pediatr Neurol. 2023</div> <div>FANNP's National Neonatal Nurse Practitioner Symposium: Clinical Update and Review, 2025 ©</div> <div>FANNP</div>			

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FIRST-LINE MANAGEMENT			
Study	Methods	Outcomes	Conclusion
Toptan (2024)	Single-center, retrospective N=104 neonates (HIE in 33%) PB 15-20 mg/kg vs LEV 30 mg/kg + additional PB 5 mg/kg or LEV 30 mg/kg PRN	Complete seizure resolution on EEG was 32.9% with PB vs 75.8% with LEV (p=0.309) Incomplete seizure resolution was similar Higher adverse effects with PB (28% vs 2%)	Complete resolution on EEG was lower with PB vs LEV, while incomplete or repeat dose was response was similar PB had higher adverse effects
Long (2024)	Single-center, retrospective N=87 neonates PB 20 mg/kg vs LEV 60 mg/kg + additional loading dose PRN	Seizure resolution (either EEG or clinical) was 27.8% PB vs 27.3% LEV (p=0.959) If failed LEV, 78.6% responded to PB If failed PB, 60.5% responded to LEV	Efficacy was similar between PB and LEV (unclear EEG vs clinical)
Khosroshahi (2025)	Open-label, parallel-group RCT N= 44 neonates in the Emergency Department (not NICU) PB 20 mg/kg + 5 mg/kg/day vs LEV 40 mg/kg + 20 mg/kg/day	Clinical seizure control within 24 hours was attained in 68.2% LEV vs 59.1% PB neonates (p=0.755)	Efficacy was similar between PB and LEV (no EEG assessment)
<div>Toptan, et al. Healthcare (Basel). 2024. Long, et al. J Pediatr Pharmacol Ther. 2024. Khosroshahi, et al. Iran J Child Neurol. 2025.</div> <div>FANNP's National Neonatal Nurse Practitioner Symposium: Clinical Update and Review, 2025 ©</div> <div>FANNP</div>			

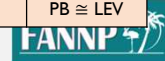
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## FIRST-LINE MANAGEMENT

- Summary of recent studies comparing phenobarbital and levetiracetam

Study	N	Design	PB dose	LEV dose	Seizure	Efficacy
Sharpe (2020)	83	Blinded RCT	20 mg/kg	40 mg/kg	EEG	PB > LEV
Thibault (2020)	53	Retrospective	20 mg/kg	30 mg/kg	EEG	PB ≅ LEV
Qiao (2021)	930	Meta-analysis	10-20 mg/kg	20-60 mg/kg	EEG	PB ≅ LEV
Verwoerd (2022)	25	Retrospective	20 mg/kg	50 mg/kg	EEG	PB ≅ LEV
Akeel (2022)	104	Blinded RCT	20 mg/kg	20 mg/kg	Clinical	PB <= LEV
Susnerwala (2022)	82	Open-Label RCT	20 mg/kg	20 mg/kg	Clinical	PB < LEV
Gyandeep (2023)	48	Open-Label RCT	15 mg/kg	40 mg/kg	Clinical	PB ≅ LEV
Bättiget (2023)	108	Retrospective	15-20 mg/kg	30 mg/kg	EEG	PB ≅ LEV
Toptan (2024)	104	Retrospective	15-20 mg/kg	30 mg/kg	EEG	PB <= LEV
Long (2024)	87	Retrospective	20 mg/kg	60 mg/kg	EEG or Clinical	PB ≅ LEV
Khosroshahi (2025)	44	Open-Label RCT	20 mg/kg	40 mg/kg	Clinical	PB ≅ LEV

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## FIRST-LINE MANAGEMENT

- ILAE Task Force on Neonatal Seizures - 2023 Update
  - FIRST LINE AGENT: Phenobarbital
- Summary of evidence:
  - Phenobarbital > phenytoin
  - Data conflicting for phenobarbital vs levetiracetam – Based on 2020 RCT by Sharpe, et al and recent guidelines → most centers back to phenobarbital

Pressler, et al. Epilepsia 2023

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## SECOND-LINE MANAGEMENT

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## SECOND-LINE MANAGEMENT

- Common options:
  - Levetiracetam
  - Phenytoin/Fosphenytoin
  - Phenobarbital (if not used first-line)

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## SECOND-LINE MANAGEMENT

- Common options:
  - Levetiracetam
  - Phenytoin/Fosphenytoin
  - Phenobarbital (if not used first-line)

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## SECOND-LINE MANAGEMENT

- Comparing the Efficacy and Safety of Levetiracetam vs Phenytoin for Treating the Acute Phase of Neonatal Seizures (2023)

Study Design	Single-blinded, case-control randomized trial
Patient Population	60 term neonates with seizures who received PB 20 mg/kg with a lack of response after 30 minutes
Intervention	Randomized to receive LEV 40-60 mg/kg or PHT 20 mg/kg loading dose
Primary Outcome	Response rates were 86.7% in LEV group and 83.3% in PHT group (p=1.0)
Secondary Outcomes	Similar rate of adverse events between groups, although slightly higher in the PHT group (6.7% and 3.3%, p=1.0)
Limitations	Specific adverse events not reported Did not include preterm infants (better overall response rates may be due to less severe seizures)
Conclusion	LEV and PHT had similar efficacy as second line therapy after phenobarbital

Mohammadi, et al. Iran J Child Neurol . 2023

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## SECOND-LINE MANAGEMENT

- Efficacy of Levetiracetam as Add-On Therapy in the Treatment of Seizures in Neonates (2024)
  - Retrospective cohort (n=47 full-term neonates)
  - Failed phenobarbital
  - Levetiracetam could be used as 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> agent
  - Monitor with EEG before, 2h, and 4h after

Rondagh, et al. Neonatology. 2024.

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## SECOND-LINE MANAGEMENT

- Efficacy of Levetiracetam as Add-On Therapy in the Treatment of Seizures in Neonates (2024)
  - First dose average 20 mg/kg
  - Total administered dose average 40 mg/kg
  - Over 80% seizure reduction in only 8/47 (17% of neonates)
    - Significantly lower than prior study
  - Seizure freedom at 24 hours only 4/47 (8.5% of neonates)

Rondagh, et al. Neonatology. 2024.

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## SECOND-LINE MANAGEMENT

- Sequential Levetiracetam and Phenytoin in Electroencephalographic Neonatal Seizures Unresponsive to Phenobarbital:A Multicenter Prospective Observational Study in India (2024)
  - Refractory to phenobarbital (n=145 with primary outcome data)
  - Given levetiracetam 20 mg/kg x 2 doses (second line)
  - Then given phenytoin 20 mg/kg x 2 doses (third line if needed)

Krishnan, et al. Lancet Reg Health Southeast Asia. 2024.

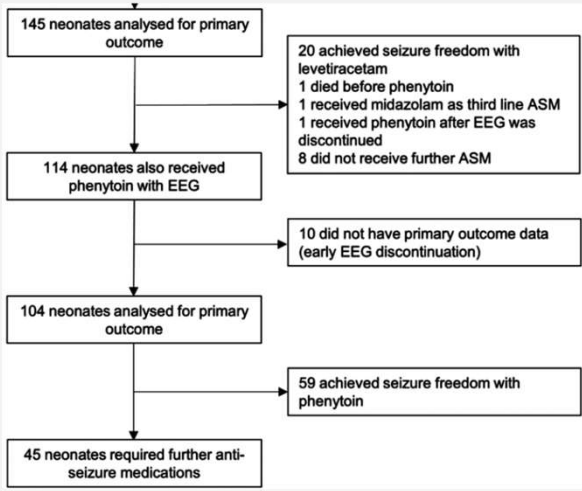
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## SECOND-LINE MANAGEMENT

- Sequential Levetiracetam and Phenytoin in Electroencephalographic Neonatal Seizures Unresponsive to Phenobarbital:A Multicenter Prospective Observational Study in India (2024)



Krishnan, et al. Lancet Reg Health Southeast Asia. 2024.

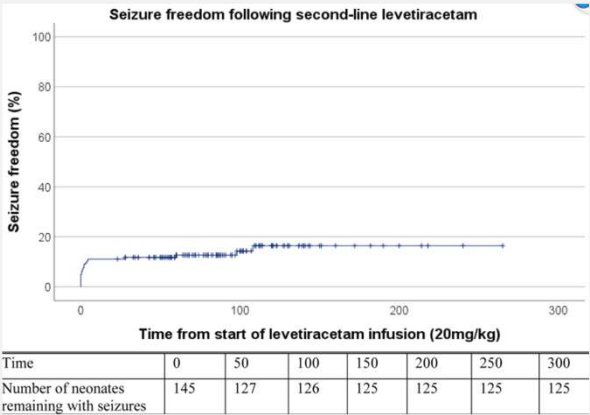
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## SECOND-LINE MANAGEMENT

- Sequential Levetiracetam and Phenytoin in Electroencephalographic Neonatal Seizures Unresponsive to Phenobarbital: A Multicenter Prospective Observational Study in India (2024)



Krishnan, et al. Lancet Reg Health Southeast Asia. 2024.

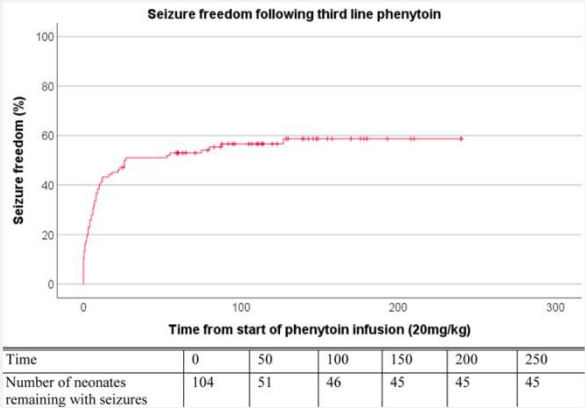
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## SECOND-LINE MANAGEMENT

- Sequential Levetiracetam and Phenytoin in Electroencephalographic Neonatal Seizures Unresponsive to Phenobarbital: A Multicenter Prospective Observational Study in India (2024)



Krishnan, et al. Lancet Reg Health Southeast Asia. 2024.

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## SECOND-LINE MANAGEMENT

- ILAE Task Force on Neonatal Seizures - 2023 Update
  - FIRST LINE AGENT: Phenobarbital
  - SECOND LINE AGENT: **Levetiracetam or Phenytoin**
    - In neonates with cardiac disorders, levetiracetam may be preferred
- Summary of evidence:
  - Data is conflicting
    - One study with similar efficacy
      - Levetiracetam efficacy in two recent studies much lower than originally reported efficacy
    - Phenytoin as 3<sup>rd</sup> line was more effective than levetiracetam as 2<sup>nd</sup> line

Pressler, et al. Epilepsia 2023

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## REFRACTORY SEIZURE MANAGEMENT

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## REFRACTORY SEIZURES

- ILAE Task Force on Neonatal Seizures - 2023 Update
  - FIRST LINE AGENT: Phenobarbital
  - SECOND LINE AGENT: Levetiracetam or Phenytoin
    - In neonats with cardiac disorders, levetiracetam may be preferred
  - OPTIONS FOR REFRACTORY SEIZURES: **midazolam or lidocaine**

Pressler, et al. Epilepsia 2023

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## REFRACTORY SEIZURES

- Midazolam

Mechanism	Enhances the inhibitory effects of GABA
Dosing	Continuous infusion: 0.1-0.4 mg/kg/hr (max reported 1.1 mg/kg/hr)
PK	Hepatic metabolism via CYP3A4 <ul style="list-style-type: none"><li>• Metabolite can accumulate in renal dysfunction</li></ul> Clearance is lower in neonates than older children/adults
TDM	Not done
Adverse Effects	Hypotension, respiratory depression, neurotoxicity
Drug Interactions	CYP3A4 substrate; concomitant CNS depressants

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## REFRACTORY SEIZURES

- Midazolam in the Treatment of Refractory Neonatal Seizures (1996)
  - Retrospective chart review (n=6)
  - Seizures refractory to phenobarbital 20-60 mg/kg + maintenance dose of 8 mg/kg/day (phenobarbital levels > 40 mcg/mL)
  - Additional 3 patients received phenytoin (total levels > 20 mcg/mL)
  - Midazolam 0.15 mg/kg loading dose + 0.1-0.4 mg/kg/hour

Sheth, et al. Clin Neuropharmacol . 1996

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## REFRACTORY SEIZURES

- Midazolam in the Treatment of Refractory Neonatal Seizures (1996)

TABLE 1. Clinical data of neonates with seizures refractory to traditional antiepileptic medication and their response to a continuous midazolam intravenous infusion

Patient	Gestation: birth weight	Etiology	PHB (µg/ml)	PHT (µg/ml)	MDZ (mg/kg/h)	Seizure frequency		Neurologic examination
						Clinical	EEG	
1	41 weeks: 3,345 g	HIE	52	20	0.1	None	None	Abnormal at 4 weeks
2	40 weeks: 3,130 g	CVT	51	20	0.3	None	None	Normal at 3 months
3	40 weeks: 3,400 g	GBS	63	23	0.1	None	↓	Abnormal at 6 weeks
4	41 weeks: 3,975 g	HIE	44	—	0.4	None	None	Normal at 6 weeks
5	30 weeks: 728 g	HIE + IVH	45	—	0.12	None	↓	Abnormal at 9 months
6	36 weeks: 3,300 g	HIE	48	—	0.2	None	None	Normal at 5 months

Overall response rate = 100%

Sheth, et al. Clin Neuropharmacol . 1996

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## REFRACTORY SEIZURES

- Midazolam in Neonatal Seizures with No Response to Phenobarbital (2005)

Study Design	Retrospective cohort study
Patient Population	45 neonates with EEG-confirmed seizures after failure to respond to PB 40 mg/kg (cumulative) and PHT 20 mg/kg
Intervention	Continuation of PB/PHT (n=32) or midazolam continuous infusion (n=13) Midazolam 0.15 mg/kg load followed by 1 mcg/kg/min (0.06 mg/kg/hr) <ul style="list-style-type: none"><li>• Titrated up to max 18 mcg/kg/min (1.1 mg/kg/hr)</li></ul>
Primary Outcome	Favorable response to treatment within the 1 <sup>st</sup> hour <ul style="list-style-type: none"><li>• 100% in midazolam group and 46.9% in the PB/PHT group (p&lt;0.01)</li></ul>
Secondary Outcomes	In neonates who were non-responders to initial treatment with PB/PHT, 53.8% of midazolam group had favorable neurologic outcomes at 1 year compared to 11.8% in the PB/PHT group (p<0.01)
Limitations	Small sample size of patients treated with midazolam Unclear what dose of PB/PHT was continued in the first group of neonates
Conclusion	Midazolam was more effective and had better long-term neurologic outcomes than continued PB/PHT in neonatal seizures refractory to initial treatment with PB/PHT

Castro Conde, et al. Neurology. 2005.

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## REFRACTORY SEIZURES

- Midazolam literature summary:
  - Efficacy 100% in studies published (very small sample sizes)
  - Doses required for seizures >>> doses for sedation
  - Concern for cognitive impairment with benzodiazepines in neonates
  - Benzodiazepines may have a role in refractory seizures

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# REFRACTORY SEIZURES

- Lidocaine

Mechanism	Inhibits sodium influx and depolarization
Dosing	Continuous infusion based on weight and body temperature (cooling vs. normothermic)
PK	Hepatic metabolism via CYP1A2 and CYP3A4 <ul style="list-style-type: none"><li>• Active metabolites MEGX and GX can accumulate and lead to CNS toxicity</li></ul>
TDM	Levels > 9 mcg/mL is associated with increased risk of cardiac toxicity
Adverse Effects	Cardiac arrhythmias, bradycardia, hypotension, methemoglobinemia
Drug Interactions	CYP1A2 and CYP3A4 substrate

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# REFRACTORY SEIZURES

- Lidocaine Response Rate in aEEG-confirmed Neonatal Seizures: Retrospective Study of 413 Full-term and Preterm Infants (2016)
  - Retrospective single-arm study (n=413)
    - Full term: n=319
    - Preterm: n=94
  - Lidocaine second-line (after phenobarbital) or third-line (after phenobarbital + midazolam, clonazepam, or phenytoin)

Weeke, et al. Epilepsia . 2016.

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## REFRACTORY SEIZURES

- Lidocaine Response Rate in aEEG-confirmed Neonatal Seizures: Retrospective Study of 413 Full-term and Preterm Infants (2016)

Table 1. Changes in lidocaine dosing regimen over the years						
Year	Bolus (mg/kg, 10 min)	Infusion I (mg/kg/h)	Infusion II (mg/kg/h)	Infusion III (mg/kg/h)	Duration of infusion (h)	Total dosage (mg/kg)
1992-2003	2	6 (24 h)	4 (12 h)	2 (12 h)	48	248
2004-2005	2	6 (12 h)	4 (12 h)	2 (12 h)	36	146
2006-2010	2	6 (6 h)	4 (12 h)	2 (12 h)	30	110
2011-2012						
Weight	Bolus (mg/kg, 10 min)	Infusion I (mg/kg/h)	Infusion II (mg/kg/h)	Infusion III (mg/kg/h)	Duration of infusion (h)	Total dosage (mg/kg)
Normothermia						
<2.5 kg	2	6 (4 h)	3 (12 h)	1.50 (12 h)	28	80
≥2.5 kg	2	7 (4 h)	3.5 (12 h)	1.75 (12 h)	28	93
Therapeutic hypothermia						
<2.5 kg	2	6 (3.5 h)	3 (12 h)	1.5 (12 h)	27.5	77
≥2.5 kg	2	7 (3.5 h)	3.5 (12 h)	1.75 (12 h)	27.5	89.5

Weeke, et al. Epilepsia . 2016.



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## REFRACTORY SEIZURES

- Lidocaine Response Rate in aEEG-confirmed Neonatal Seizures: Retrospective Study of 413 Full-term and Preterm Infants (2016)

Lidocaine	Good Response	Intermediate Response	Overall Response
2 <sup>nd</sup> line	21.4%	51.1%	72.5%
3 <sup>rd</sup> line	67.6%	12.4%	80%

- Lower response rate in preterm compared to term neonates
- Better response to lidocaine if seizure etiology was stroke or ICH
- Better response if patient was hypothermic compared to normothermic

Weeke, et al. Epilepsia . 2016.



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## REFRACTORY SEIZURES

- Lidocaine as Treatment for Neonatal Seizures: Evaluation of Previously Developed Population Pharmacokinetic Models and Dosing Regimen (2020)
  - Multicenter, prospective cohort (n=92)
    - Full-term: n=64 (n=28 were therapeutic hypothermia)
    - Preterm: n=28
  - Lidocaine was second- or third-line for seizures refractory to midazolam and/or phenobarbital

Favié, et al. Br J Clin Pharmacol . 2020

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## REFRACTORY SEIZURES

- Lidocaine as Treatment for Neonatal Seizures: Evaluation of Previously Developed Population Pharmacokinetic Models and Dosing Regimen (2020)

TABLE 1 Proposed lidocaine dosing regimen<sup>33,34</sup>

Weight	Bolus		Loading phase		Maintenance phase I		Maintenance phase II	
	Dose	Duration	Dose	Duration	Dose	Duration	Dose	Duration
Normothermia								
< 1.6 kg	2 mg/kg	10 min	5 mg/kg	4 h	2.5 mg/kg	12 h	1.25 mg/kg	12 h
1.6–2.6 kg	2 mg/kg	10 min	6 mg/kg	4 h	3 mg/kg	12 h	1.5 mg/kg	12 h
> 2.6 kg	2 mg/kg	10 min	7 mg/kg	4 h	3.5 mg/kg	12 h	1.75 mg/kg	12 h
Hypothermia								
< 2.5 kg	2 mg/kg	10 min	6 mg/kg	3.5 h	3 mg/kg	12 h	1.5 mg/kg	12 h
≥ 2.5 kg	2 mg/kg	10 min	7 mg/kg	3.5 h	3.5 mg/kg	12 h	1.75 mg/kg	12 h

Favié, et al. Br J Clin Pharmacol . 2020

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## REFRACTORY SEIZURES

- Lidocaine as Treatment for Neonatal Seizures: Evaluation of Previously Developed Population Pharmacokinetic Models and Dosing Regimen (2020)
  - PK results:
    - Lower clearance with lower PMA (e.g., clearance at 25 weeks PMA was 90% lower than 40 weeks PMA)
    - Serum concentration were > 9 mcg/mL more often in neonates undergoing therapeutic hypothermia

Favié, et al. Br J Clin Pharmacol . 2020

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## REFRACTORY SEIZURES

- Lidocaine as Treatment for Neonatal Seizures: Evaluation of Previously Developed Population Pharmacokinetic Models and Dosing Regimen (2020)
  - Efficacy:
    - Lidocaine effective in 56.5% of neonates
    - Highest efficacy in term, normothermic neonates
    - No difference in lidocaine levels between responders and non-responders

Favié, et al. Br J Clin Pharmacol . 2020

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## REFRACTORY SEIZURES

- Lidocaine literature summary:
  - Efficacy ranged from 56.5% to 80%
    - Studies included neonates undergoing therapeutic hypothermia
  - Not frequently used in practice
  - Concerns for cardiotoxicity
    - Requires therapeutic drug monitoring

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## REFRACTORY SEIZURES

- Comparison of Continuous Drip of Midazolam or Lidocaine in the Treatment of Intractable Neonatal Seizures (2007)
  - Retrospective chart review (n=30)
  - Seizures from HIE
  - Refractory to first-line treatment
  - Dosing:
    - Lidocaine 2 mg/kg over 20 minutes + 4-6 mg/kg/hour
    - Midazolam 0.06-0.2 mg/kg/hour

Shany, et al. J Child Neurol. 2007

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## REFRACTORY SEIZURES

- Comparison of Continuous Drip of Midazolam or Lidocaine in the Treatment of Intractable Neonatal Seizures (2007)

	Good Response	Partial Response	Overall Response
Lidocaine (n=22)	50%	27%	77%
Midazolam (n=8)	0%	50%	50%

- Lidocaine given to 5 midazolam non-responders → all had partial or complete response to lidocaine
- Midazolam given to 4 lidocaine non-responders → all had a partial or complete response to midazolam

Shany, et al. J Child Neurol. 2007

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## REFRACTORY SEIZURES

- Efficacy of Levetiracetam as Add-On Therapy in the Treatment of Seizures in Neonates (2024)
  - *Previously reported this study – also compared outcomes to midazolam and lidocaine*
  - Retrospective cohort (n=47 full-term neonates)
  - Failed phenobarbital
  - Stage in therapy:
    - Midazolam (2<sup>nd</sup> line n=20; 3<sup>rd</sup> line n=6)
    - Lidocaine (3<sup>rd</sup> line n=7, 4<sup>th</sup> line n=18)
  - Monitored with EEG before, 2h, and 4h after

Rondagh, et al. Neonatology. 2024.

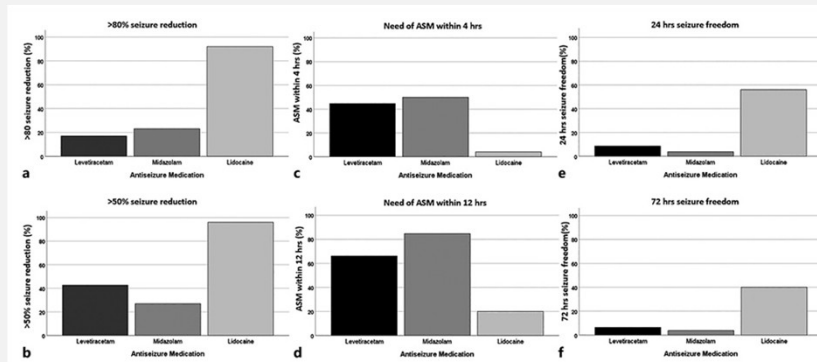
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## REFRACTORY SEIZURES

- Efficacy of Levetiracetam as Add-On Therapy in the Treatment of Seizures in Neonates (2024)



Rondagh, et al. Neonatology. 2024.

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## REFRACTORY SEIZURES

- Summary of review:
  - Midazolam or lidocaine are recommended agents for refractory seizures by the 2023 ILAE guidelines
- Limited comparative data:
  - Data conflicting with either similar efficacy or superiority of lidocaine
  - Patients who fail to respond to one may respond to other
  - Safety concerns with lidocaine
  - Probably more familiarity among NICU staff with midazolam

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## REFRACTORY SEIZURES

- Other Therapies:

Lacosamide

Topiramate

Carbamazepine

Bumetanide


Inhaled xenon

Ketogenic diet

Ketamine

Pyridoxine

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## PROPOSED TREATMENT ALGORITHM

1<sup>st</sup> Line:  
Phenobarbital

2<sup>nd</sup> Line:  
Levetiracetam  
or Fosphenytoin

3<sup>rd</sup> Line:  
Fosphenytoin or  
Levetiracetam


Refractory:  
Midazolam

Refractory:  
Lidocaine or  
other agents

Trial: Pyridoxine

Our practice:  
Lacosamide  
Ketamine

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## REFRACTORY SEIZURES

- Channelopathies
  - ILAE 2023 guidelines mention alternative therapies if family history of channelopathies
    - Most commonly mutations in the KCNQ2 and SCN2A genes, and to a lesser extent in the KCNQ3 gene
    - Affect ion channels, usually voltage-gated Na, K, and calcium

Channelopathy	
Age of seizure onset	Newborn (1–2 weeks after birth)
Brain involvement	Positive
Seizure frequencies	+ to +++
EEG	Unremarkable to severe suppression-burst
MRI at age of seizure onset	Unremarkable
MRI at follow up after first seizure	Brain atrophy (if not treated)

Lee I, et al. *Life (Basel)*. 2021.  
Pijpers JA, et al. *Seizure: Eur J Epilepsy*. 2023



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## REFRACTORY SEIZURES

- Channelopathies
  - ILAE 2023 guidelines mention alternative therapies if family history of channelopathies
    - Treatments: sodium channel blockers (phenytoin, carbamazepine, oxcarbazepine, lidocaine)
      - May require higher doses than typical neonatal seizures

Lee I, et al. *Life (Basel)*. 2021.  
Pijpers JA, et al. *Seizure: Eur J Epilepsy*. 2023



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## PRACTICAL CONSIDERATIONS

- Availability in automated dispensing cabinets for loading doses and administered on syringe pump:

Drug	Vial Concentration	Preparation	Administration
Phenobarbital	10 mg/mL, <b>65 mg/mL</b> , 130 mg/mL	Straight draw from vial	Max 1 mg/kg/min (20 mg/kg over 20 min)
Levetiracetam	100 mg/mL	Straight draw from vial	Over 5 minutes
Fosphenytoin	50 mgPE/mL	Dilute 1:1 with NS to final concentration 25 mgPE/mL	Max 2 mgPE/kg/min (20 mg/kg over 10 min)

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## VITAMIN-RESPONSIVE METABOLIC SEIZURES

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## VITAMIN-RESPONSIVE METABOLIC SEIZURES

- Some neonatal seizures are metabolic in nature and can be treated with vitamins

Neonatal-Onset Seizures of Metabolic Origin

Type	Characteristic Features	Diagnosis	Treatment
Pyridoxine-dependent epilepsy	Seizures refractory to common AEDs, hypothermia	Low α-AASA and pipercolic acid	Pyridoxine
	Dystonia	ALDH7A1 gene testing	
PNPO deficiency		Low CSF PLP	PLP
		PNPO gene testing	
Folinic acid-responsive seizures	Seizures refractory to common AEDs	ALDH7A1/FOLR1 gene testing	Folinic acid
	Transient response to pyridoxine		
Biotinidase deficiency	Alopecia, skin rash	Biotinidase enzyme analysis	Biotin
	Hearing and vision abnormalities	BTB sequencing	
	Hypotonia		

Kaur, et al. NeoReviews. 2020.



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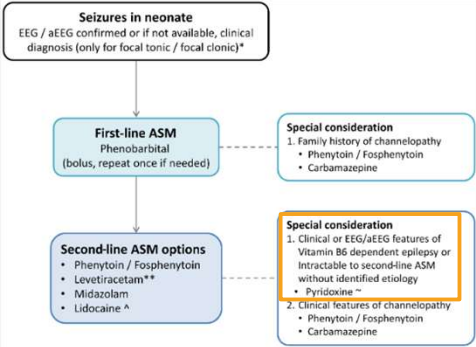
## VITAMIN-RESPONSIVE METABOLIC SEIZURES

- Should be considered in neonates refractory to standard antiepileptic drug therapy
- ILAE 2023 Guidelines mention pyridoxine + pyridoxal 5'-phosphate (PLP)

### Consensus-based recommendations

A trial of pyridoxine (add-on to ASM) may be attempted in neonates presenting with clinical features or EEG characteristics suggestive of vitamin B6-dependent epilepsy and neonates with seizures unresponsive to second-line ASM without an identified etiology.

Level of agreement: High.



Pressler, et al. Epilepsia. 2023.



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## PYRIDOXINE-DEPENDENT EPILEPSY

- Typical neonatal onset pyridoxine-dependent epilepsy occurs in the first few days of life (some even detected in utero)
- Intractable seizures unresponsive to conventional treatment
  - Clonic seizures (focal and multifocal)
  - Tonic-clonic seizures
  - Generalized seizures
  - Abnormal movements
- Nearly 75% of patients have intellectual or developmental delay, even those with early treatment and diagnosis.

Coughlin, et al. J Inherit Metab Dis. 2020.  
Kaur, et al. NeoReviews. 2020.  
Pressler, et al. Epilepsia. 2023.  
Yang, et al. Epilepsy & Behavior. 2023.

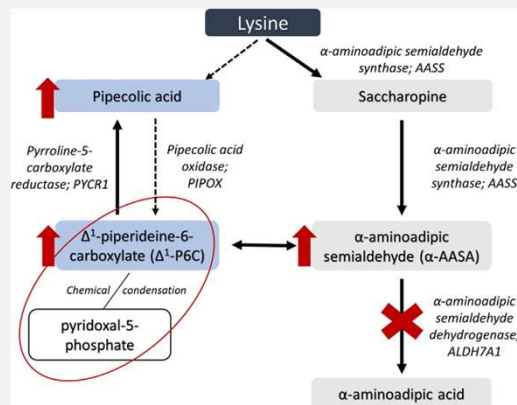
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## PYRIDOXINE-DEPENDENT EPILEPSY

- Most common: mutation in the *ALDH 7A1* gene (autosomal recessive)



Coughlin, et al. J Inherit Metab Dis. 2020.  
Kaur, et al. NeoReviews. 2020.  
Pressler, et al. Epilepsia. 2023.  
Yang, et al. Epilepsy & Behavior. 2023.

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## PYRIDOXINE-DEPENDENT EPILEPSY

- Most common: mutation in the *ALDH 7A1* gene (autosomal recessive)
- Other causes that may response to pyridoxine:
  - Hypophosphatasia
  - Hyperphosphatasia
  - Pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency
  - PLP binding protein deficiency (formerly called PROSC deficiency)

Coughlin, et al. J Inherit Metab Dis. 2020.  
Kaur, et al. NeoReviews. 2020.  
Pressler, et al. Epilepsia. 2023.  
Yang, et al. Epilepsy & Behavior. 2023.

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## PYRIDOXINE-DEPENDENT EPILEPSY

- Most common: mutation in the *ALDH 7A1* gene (autosomal recessive)
- Once disorder is established, lysine free diets can be beneficial
  - Breastmilk is low in lysine – continue to breastfeed
  - Special lysine-free formulas can be prescribed
  - Low lysine: cereal, fruits, vegetables
  - High lysine: meat and animal protein

Van Karnebeek, et al. J Inherit Metab Dis. 2014.

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## PYRIDOXINE-DEPENDENT EPILEPSY

- Treatment: pyridoxine and/or pyridoxal 5'-phosphate (PLP)
  - Pyridoxine
    - Loading Dose: 100 mg = 1 vial
    - Repeat doses not mentioned in ILAE Guideline
      - Many experts give repeat doses up to 5 total
      - My practice: 100 mg x 3 doses
    - Slow IV push
    - Maintenance Dose: 15 mg/kg/dose BID IV or PO
    - Monitor for respiratory depression
    - Some patients with delayed response → continue for at least 3-5 days for trial



Coughlin, et al. J Inherit Metab Dis. 2020.  
Kaur, et al. NeoReviews. 2020.  
Pressler, et al. Epilepsia. 2023.  
Yang, et al. Epilepsy & Behavior. 2023.

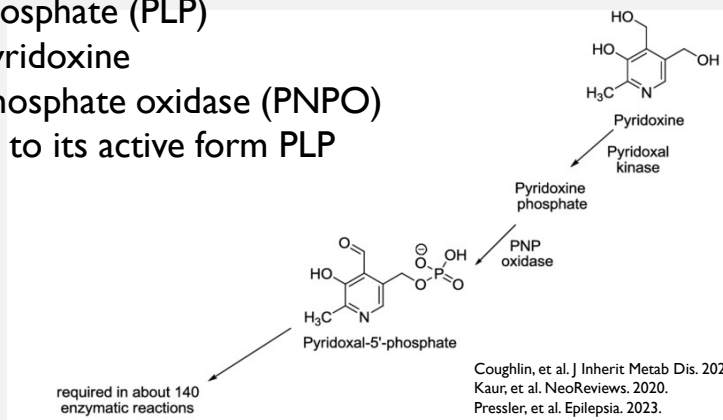


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## PYRIDOXINE-DEPENDENT EPILEPSY AND PNPO DEFICIENCY

- Treatment: pyridoxal 5'-phosphate (PLP)
  - PLP = active form of pyridoxine
    - Pyridox(am)ine 5-phosphate oxidase (PNPO) converts pyridoxine to its active form PLP



Coughlin, et al. J Inherit Metab Dis. 2020.  
Kaur, et al. NeoReviews. 2020.  
Pressler, et al. Epilepsia. 2023.  
Yang, et al. Epilepsy & Behavior. 2023.



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## PYRIDOXINE-DEPENDENT EPILEPSY AND PNPO DEFICIENCY

- Treatment: pyridoxal 5'-phosphate (PLP)
  - PLP = active form of pyridoxine
    - PNPO deficiency often presents as fetal distress in late pregnancy
    - Seizures start within first few days of life
    - If untreated, cases are generally fatal in the first year of life

Coughlin, et al. J Inherit Metab Dis. 2020.  
Kaur, et al. NeoReviews. 2020.  
Pressler, et al. Epilepsia. 2023.  
Yang, et al. Epilepsy & Behavior. 2023.

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## PYRIDOXINE-DEPENDENT EPILEPSY AND PNPO DEFICIENCY

- Treatment: pyridoxal 5'-phosphate (PLP)
  - PLP = active form of pyridoxine
    - Most neonates with PNPO deficiency respond to PLP only and not pyridoxine
    - Dose: 30 mg/kg/day in 3 divided doses
    - Biggest problem: no FDA approved product!

Coughlin, et al. J Inherit Metab Dis. 2020.  
Kaur, et al. NeoReviews. 2020.  
Pressler, et al. Epilepsia. 2023.  
Yang, et al. Epilepsy & Behavior. 2023.

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## PYRIDOXINE-DEPENDENT EPILEPSY AND PNPO DEFICIENCY

- Treatment: pyridoxal 5'-phosphate (PLP)
  - Options to obtain:
    - Family could purchase through commercial retailers of OTC vitamins and bring to hospital (also called P5P)
    - Some hospitals can acquire medical grade powder
  - Continue pyridoxine while awaiting arrival of PLP



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## FOLINIC ACID-RESPONSIVE SEIZURES

- Folinic acid (5-formyltetrahydrofolate) = active metabolite of folic acid
- Similar presentation to pyridoxine-responsive epilepsy
  - Mutations in the same *ADH 7A1* gene
  - Sometimes can initially respond to pyridoxine but is transient
- Usually present in the first few days of life
  - Intrauterine hiccups can be noted
  - Myoclonic or clonic
  - Often with apnea
- Fatal if left untreated

Kaur, et al. NeoReviews. 2020.  
Nicolai, et al. Pediatr Neurol. 2006.  
Yang, et al. Epilepsy & Behavior. 2023.

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## FOLINIC ACID-RESPONSIVE SEIZURES

- Serum and CSF level of 5-methyltetrahydrofolate are normal
- Diagnosis can be made based on a compound (not yet identified) found on high-performance liquid chromatography in the CSF
  - Disease-specific marker
  - 50-75% decrease of CSF disease-specific marker after treatment

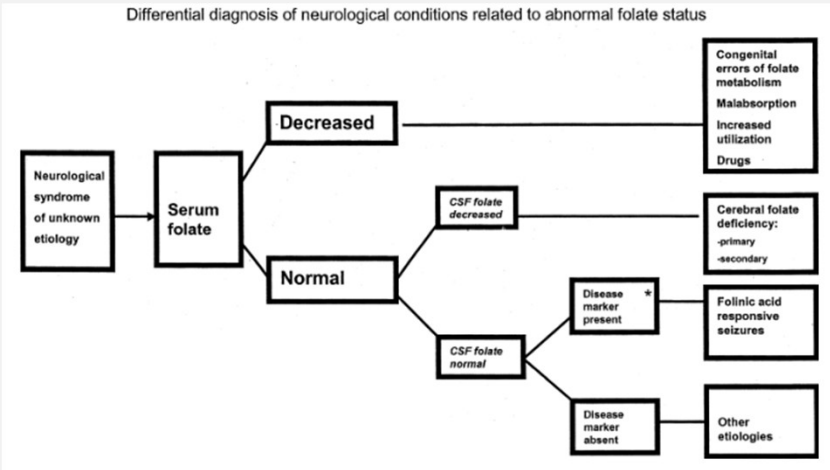
Kaur, et al. NeoReviews. 2020.  
Nicolai, et al. Pediatr Neurol. 2006.  
Yang, et al. Epilepsy & Behavior. 2023.



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## FOLINIC ACID-RESPONSIVE SEIZURES



Djukic. Pediatr Neurol. 2007.



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## FOLINIC ACID-RESPONSIVE SEIZURES

- Almost immediate response to folinic acid supplementation
  - Dose: 2.5 to 5 mg twice daily (or 1.5 to 5 mg/kg/day)
  - May require up-titration up to 8 mg/kg/day
  - FDA-approved medication: leucovorin tablets and injections



Kaur, et al. NeoReviews. 2020.  
Nicolai, et al. Pediatr Neurol. 2006.  
Yang, et al. Epilepsy & Behavior. 2023.



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## BIOTINIDASE DEFICIENCY SEIZURES

- Autosomal recessive neurocutaneous disorder
  - Mutations in *BTD* gene encoding biotinase
  - Over half of cases from homozygous c.98-104del7ins3 mutation
  - ~20% of cases have parental consanguinity
- Reduced ability of intestine to absorb biotin
  - Profound deficiency (<10% of normal serum biotinidase activity): presents early, usually with clonic seizures
  - Partial deficiency (10-30% of normal serum biotinidase activity): may present from infancy to adulthood

Yang, et al. Epilepsy & Behavior. 2023.



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## BIOTINIDASE DEFICIENCY SEIZURES

- Autosomal recessive neurocutaneous disorder
  - Skin manifestations: eczematous rash and alopecia



Rajendiran, et al. BMJ Case Reports. 2011.  
Tomar, et al. Med J Armed Forces India. 2012.  
Yang, et al. Epilepsy & Behavior. 2023.

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## BIOTINIDASE DEFICIENCY SEIZURES

- Treatment: Biotin 5-20 mg daily (no FDA-approved IV formulation)
  - Many different brands
  - Typically respond within hours to days with supplementation



Rajendiran, et al. BMJ Case Reports. 2011.  
Tomar, et al. Med J Armed Forces India. 2012.  
Yang, et al. Epilepsy & Behavior. 2023.

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# VITAMIN-RESPONSIVE METABOLIC SEIZURES

- Example Treatment Algorithm

Neonatal seizures unresponsive to conventional antiepileptic medications

Pyridoxine trial<sup>a</sup>  
100 mg IV or 15 to 30 mg/kg per day orally divided 3 times per day for 2 to 3 days

Clinical or EEG response?

Yes: Chronic supplementation with pyridoxine

No: PLP trial  
60 mg/kg/day orally in 3 divided doses for 2 to 3 days

Clinical or EEG response?

Yes: Chronic supplementation with pyridoxine

No: Leucovorin trial  
2.5 mg IV

Clinical or EEG response?

Yes: Chronic supplementation with pyridoxine

No: Was biotinidase deficiency excluded by newborn screen?

Yes: Biotin trial  
10 mg orally

Clinical or EEG response?

Yes: Chronic supplementation with pyridoxine

No: Confirm with biotinidase activity in serum (deficient) or BTD genetic analysis

Confirmed: Chronic supplementation with pyridoxine

Not confirmed: Consider evaluation and genetic testing for alternative diagnoses (eg, inborn errors of metabolism, channelopathies)

Treatment of Neonatal Seizures. UpToDate.

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# VITAMIN-RESPONSIVE METABOLIC SEIZURES

- What does this look like at my institution for refractory seizures?
  - Early trial of therapies while further genetic and other diagnostic testing is ongoing

Pyridoxine 100 mg IV x 3 doses

If response: start maintenance pyridoxine

If no response: trial vitamin cocktail

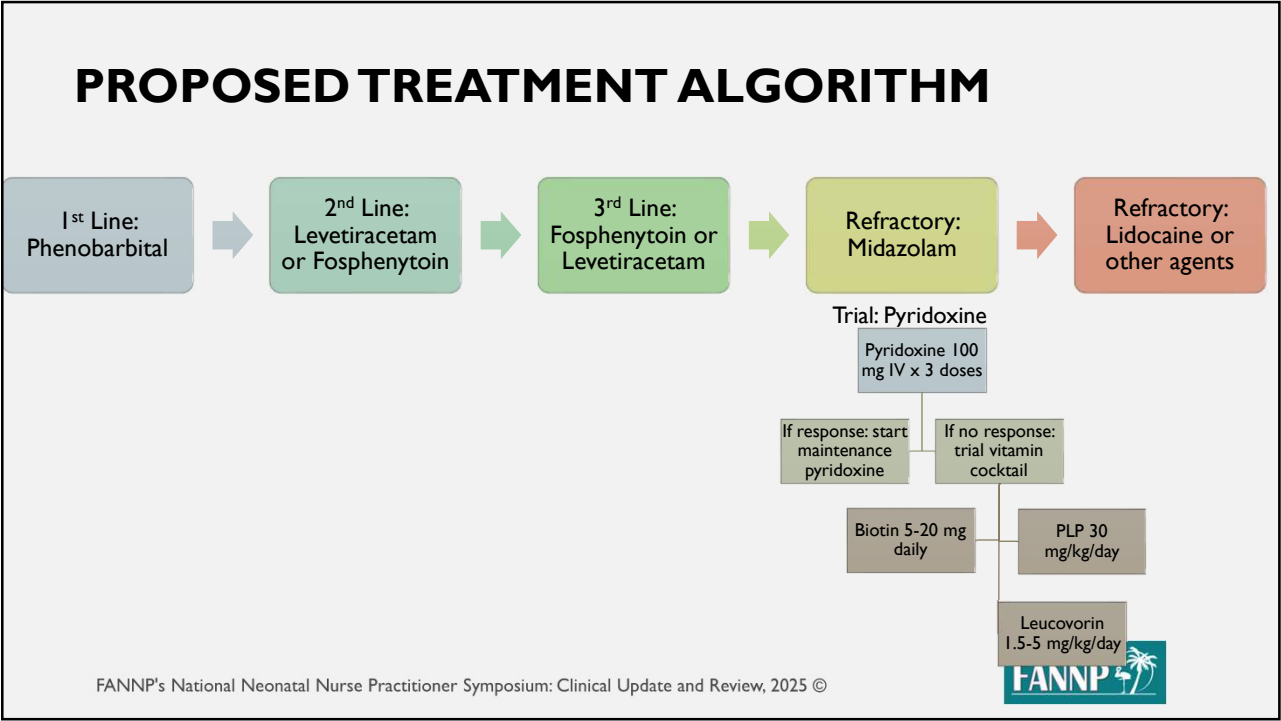
Biotin 5-20 mg daily

PLP 30 mg/kg/day

Leucovorin 1.5-5 mg/kg/day

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**KEY TAKEAWAYS**

- The pathophysiology and manifestations of neonatal seizures is unique and must be treated differently than seizures in older patients
- The optimal antiepileptic regimen for neonatal seizures is still under debate, although more recent data with levetiracetam is challenging the tradition of phenobarbital as first line
- Therapies for refractory treatment have limited definitive data, and some patients may respond to different refractory treatment
- Vitamin-responsive seizures should be considered for neonates refractive to traditional therapies

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# **STATUS UPDATES ON NEONATAL SEIZURES AND STATUS EPILEPTICUS**

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