# 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™ 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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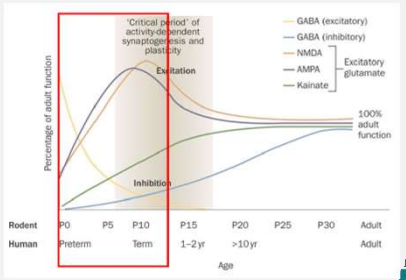
## PATHOPHYSIOLOGY




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



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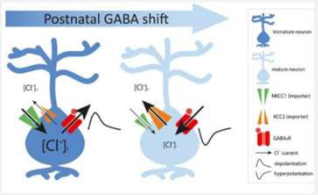
## PATHOPHYSIOLOGY

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




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



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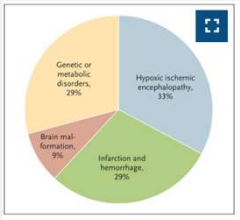
## ETIOLOGY

- **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 |

[a] 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 |

[a] CSF denotes cerebrospinal fluid, HIE hypoxemic 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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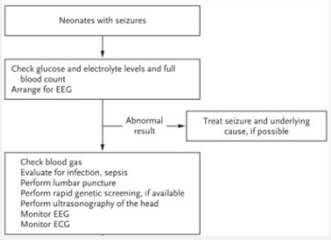
## HISTORY OF ANTIEPILEPTIC DRUGS




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



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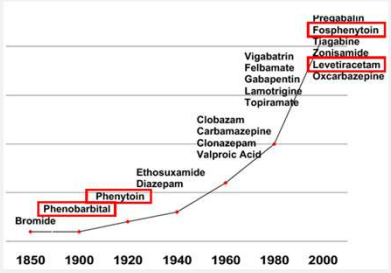
## HISTORY OF ANTIEPILEPTIC DRUGS




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)<br>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<br>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<br>Maintenance: 4-8 mgPE/kg/day divided BID |
| PK | Highly protein bound<br>• Neonates have less plasma proteins |
| TDM | Goal: 8-15 mcg/mL (total), 1-2 mcg/mL (free)<br>• Lower total PHT goal than older children/adults<br>• Free PHT level may be more reliable |
| Adverse Effects | Hypotension, cardiac arrhythmias<br>• Max rate 2 mgPE/kg/min (up to 150 mgPE/min)<br>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<br>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 | • The severity of initial seizure activity was inversely related to the successful control of seizures in both groups<br>• No significant changes in heart rate, rhythm, MAP or respiratory status were reported in either group |

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<br>Concentration of PB in the study was moderately therapeutic compared to supratherapeutic levels of PHT<br>• Plasma concentrations of **25 mcg/mL (PB)** and **3 mcg/mL (free PHT)** |
| 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, PB would likely have been superior to PHT** |

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



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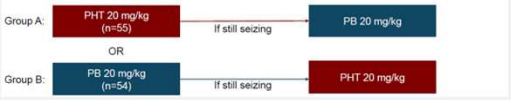
## FIRST-LINE MANAGEMENT

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

| | |
|---|---|
| Study Design | Open-label, randomized control trial |
| Patient Population | 109 neonates ≥ 35 weeks GA with clinical seizures |
| Intervention | Randomization to PHT or PB |




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<br>• After initial 20 mg/kg loading dose: **72.2% in PB group** vs **14.5% in PHT group (p<0.001)**<br>• After crossover to the opposite drug: **96.3% in PB group** vs **80%in PHT group (p<0.05)** |
| 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<br>Did not include preterm neonates |
| Conclusion | • **PB is more efficacious than PHT in control of clinical seizures**<br>• **In neonates who received PHT as first line, after crossing over to receive PB the cessation of seizures increased by 65.5%**<br>• **Doses > 20 mg/kg of PB may be required to improve response** |

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<br>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<br>• May have beneficial effects on neurologic outcomes |
| 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 | 2.097 | 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 | 30/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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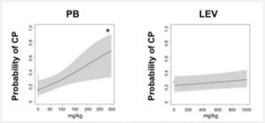
## FIRST-LINE MANAGEMENT

- 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 ≥ 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)**

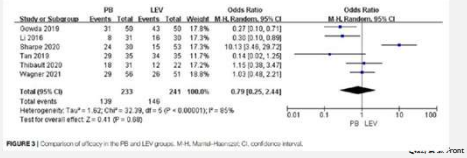


FIGURE 3 | Comparison of efficacy in the PB and LEV groups. M-H, Mantel-Haenszel; CI, confidence interval.

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)

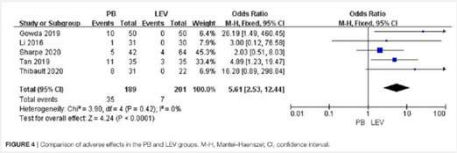


FIGURE 4 | Comparison of adverse effects in the PB and LEV groups. M-H, Mantel-Haenszel; CI, confidence interval.

Qiao, et al. Front Neurol. 2021.



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## FIRST-LINE MANAGEMENT

| Study | Methods | Outcomes | Conclusion |
|---|---|---|---|
| Thibault (2020) | Retrospective, single-center<br>N=53 post-op cardiac surgery<br>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<br>N=25<br>PB 20 mg/kg vs. LEV 50 mg/kg | Sustained seizure burden on EEG < 10% in 65% LEV and 63% PB<br>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<br>N=104<br>PB 20 mg/kg vs. LEV 20 mg/kg<br>+/-additional 10 mg/kg if needed | Clinical seizure cessation maintained for 24 hours in 65.4% PB and 78.8% LEV (p=0.01)<br>No adverse events in LEV group vs. 12 events in PB group<br>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<br>N=82 asphyxiated neonates<br>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<br>N=48 preterm neonates<br>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<br>N=108 preterm and term neonates<br>PB 15-20 mg/kg vs LEV 30 mg/kg | Complete response on EEG in 36% PB and 45% LEV (p=0.4)<br>Partial response on EEG in 64% PB and 55% LEV<br>Adverse effects in 24% PB and 1% LEV (hypotension, respiratory depression) (p<0.001) | Efficacy was similar between PB and LEV<br>Significantly more adverse events in the PB group than LEV group |

Susnerwala, et al . Hosp Pediatr . 2022
Gyandeep, et al. Eur J Pediatr 2023
Bättig, et al. Pediatr Neurol. 2023



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## FIRST-LINE MANAGEMENT

| Study | Methods | Outcomes | Conclusion |
|---|---|---|---|
| Toptan (2024) | Single-center, retrospective<br>N=104 neonates (HIE in 33%)<br>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)<br>Incomplete seizure resolution was similar<br>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<br>PB had higher adverse effects |
| Long (2024) | Single-center, retrospective<br>N=87 neonates<br>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)<br>If failed LEV, 78.6% responded to PB<br>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<br>N= 44 neonates in the Emergency Department (not NICU)<br>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) |

Toptan, et al. Healthcare (Basel). 2024.
Long, et al. J Pediatr Pharmacol Ther. 2024.
Khosroshahi., et al. Iran J Child Neurol. 2025.



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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<br>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 2nd, 3rd, or 4th 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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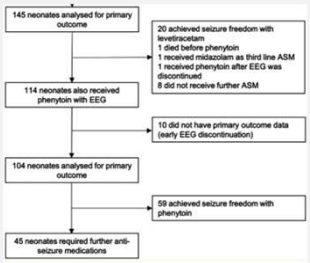
## SECOND-LINE MANAGEMENT

- 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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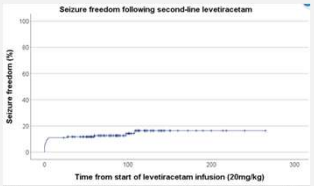
## SECOND-LINE MANAGEMENT

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




| Time | 0 | 50 | 100 | 150 | 200 | 250 | 300 |
|---|---|---|---|---|---|---|---|
| Number of neonates remaining with seizures | 145 | 127 | 126 | 125 | 125 | 125 | 125 |

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



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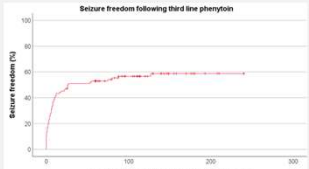
## SECOND-LINE MANAGEMENT

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




| Time | 0 | 50 | 100 | 150 | 200 | 250 |
|---|---|---|---|---|---|---|
| Number of neonates remaining with seizures | 104 | 51 | 46 | 45 | 45 | 45 |

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 3rd line was more effective than levetiracetam as 2nd 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<br>• Metabolite can accumulate in renal dysfunction<br>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: Clinical | Seizure frequency: EEG | Neurologic examination |
|---|---|---|---|---|---|---|---|---|
| 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)<br>Midazolam 0.15 mg/kg load followed by 1 mcg/kg/min (0.06 mg/kg/hr)<br>• Titrated up to max 18 mcg/kg/min (1.1 mg/kg/hr) |
| **Primary Outcome** | Favorable response to treatment within the 1st hour<br>• 100% in midazolam group and 46.9% in the PB/PHT group (p<0.01) |
| **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<br>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<br>• Active metabolites MEGX and GX can accumulate and lead to CNS toxicity |
| **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 |
|---|---|---|---|
| 2nd line | 21.4% | 51.1% | 72.5% |
| 3rd 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[33,34]

| | Bolus | | Loading phase | | Maintenance phase I | | Maintenance phase II | |
|---|---|---|---|---|---|---|---|---|
| **Weight** | **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
    - Midazolem 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 (2nd line n=20; 3rd line n=6)
    - Lidocaine (3rd line n=7, 4th line n=18)
  - Monitored with EEG before, 2h, and 4h after

Rondagh, et al. Neonatology. 2024.



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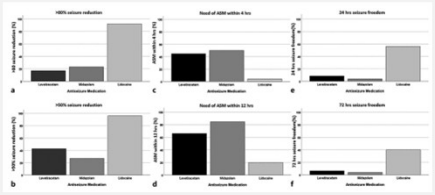
## REFRACTORY SEIZURES

- 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

1st Line: Phenobarbital → 2nd Line: Levetiracetam or Fosphenytoin → 3rd Line: Fosphenytoin or Levetiracetam → Refractory: Midazolam → Refractory: Lidocaine or other agents

Trial: Pyridoxine

Our practice: Lacosamide Ketamine



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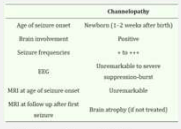
## REFRACTORY SEIZURES

- 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.
Pipper 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.
Pipper 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, **65 mg/mL**, 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 pipecolic 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 | *BTD* sequencing | |
| | Hypotonia | | |

Kaur, et al. NeoReviews. 2020.



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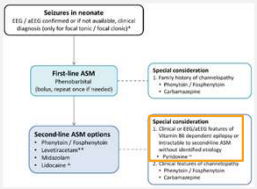
## VITAMIN-RESPONSIVE METABOLIC SEIZURES

- 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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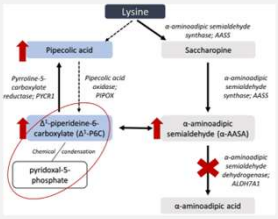
## PYRIDOXINE-DEPENDENT EPILEPSY

- 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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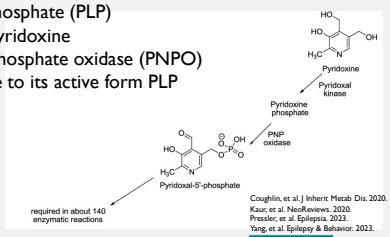
## PYRIDOXINE-DEPENDENT EPILEPSY AND PNPO DEFICIENCY

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

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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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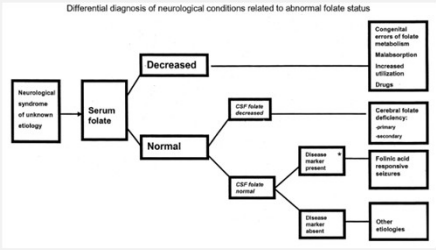
## FOLINIC ACID-RESPONSIVE SEIZURES




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 DEFICENCY 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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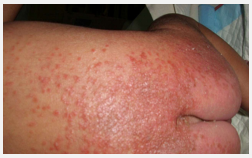
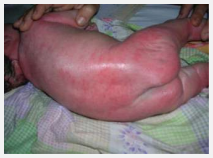
## BIOTINIDASE DEFICENCY SEIZURES

- 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 DEFICENCY 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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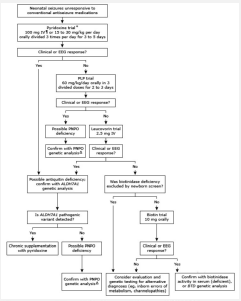
## VITAMIN-RESPONSIVE METABOLIC SEIZURES

- Example Treatment Algorithm



Treatment of Neonatal Seizures. UpToDate.



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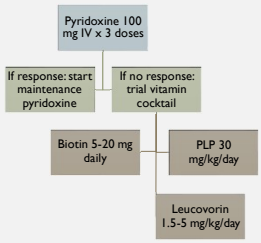
## VITAMIN-RESPONSIVE METABOLIC SEIZURES

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



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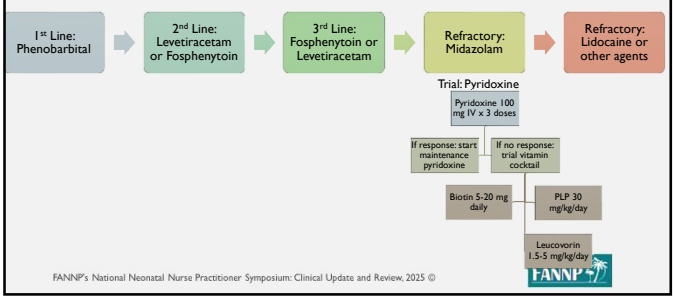
## PROPOSED TREATMENT ALGORITHM



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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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