Learning Objectives:

1. Describe the epidemiology, pathophysiology, and diagnosis of neonatal seizures.
2. Examine current pharmacologic options and the management algorithm for neonatal seizures.
3. Evaluate available evidence describing the safety and efficacy of levetiracetam (LEV) versus phenobarbital in patients with neonatal seizure.
4. Apply evidence-based findings and provide appropriate treatment recommendations regarding the management of neonatal seizures.
Neonatal Seizures

I. Definition and Epidemiology
   a. Seizures are an excessive and repetitive electrical discharge in the central nervous system (CNS)
      i. Highest frequency of seizures is during the neonatal period
   b. Most common neurological emergency in newborns
   c. Exact incidence is unknown due to difficulty in diagnosis and subtle presentations
      i. Estimated 1.8 per 1000 live births in the United States (US)

II. Pathophysiology
   a. Mechanisms of seizures in newborns is not well understood [Appendix A]
   b. Theorized that newborns are especially susceptible to seizures due to:
      i. Enhanced cellular and synaptic excitation
      ii. Relative lack of inhibitory receptors and neurotransmitters
      iii. Enhanced propagation of epileptic activity
   c. Imbalance between excitation and inhibition pathways in neonatal brain
   d. Controversy exists over whether seizures themselves cause damage to the developing brain, or if the damage is due to the underlying cause of the seizure

III. Etiology
   a. Result of underlying disease processes, metabolic abnormalities, or structural anomalies
   b. Two-thirds of all cases are due to hypoxic-ischemic encephalopathy (HIE) caused by perinatal asphyxia
   c. Primary etiologic factor may not be clear as many infants may have multiple factors [Appendix B]
      i. Ex: HIE and hypoglycemia present simultaneously
   d. Differential diagnoses can be classified based upon the time to peak onset of symptoms [Appendix C]
   e. Only 2-5% of neonatal seizures are idiopathic

IV. Risk factors
   a. Pre-term infants (less than 38 weeks gestational age)
      i. Estimated 9% increase in seizure for each week of decrease in gestational age
   b. Low birth weight (less than 2.5 kg)
   c. Male gender
   d. Respiratory complications or respiratory distress
   e. Patent ductus arteriosus
   f. Necrotizing enterocolitis
   g. Periventricular leukomalacia
   h. Intraventricular hemorrhage
   i. Surgery

V. Diagnosis
   a. Dependent on familial predisposition, clinical presentation, and electroencephalogram (EEG) findings
   b. Often difficult diagnosis and not always caught
   c. EEG
      i. May not detect subtle, generalized tonic, or myoclonic seizures
      ii. Able to detect some subclinical seizures
         1. Preterm neonates:
            a. 66% have at least one subclinical seizure
            b. 24% have exclusively subclinical seizures
      iii. Used to detect the presence/absence of seizures, not the etiology
d. Classifications of neonatal seizures:
   i. Focal clonic: begin on one side of the body and can involve the limbs and/or one side of
      the neck, trunk, or face; may include other body parts on the same side
   ii. Multi-focal clonic: migratory in nature
   iii. Generalized tonic: sustained posturing rigidity

VI. Prognosis
   a. Mortality risk:
      i. Preterm neonates: 22-58%
      ii. Term neonates: ~15%
   b. Risk of neurologic impairment: 30%
   c. Most important determinant of prognosis is the underlying etiology
### Treatment

I. **Guidelines**
   a. No specific guidelines for treatment of neonatal seizures from a US-based association
   b. 2011: World Health Organization (WHO) released guidelines for neonatal seizures
      i. Majority of recommendations are based on weak evidence due to lack of evidence-based data from clinical studies
      ii. Since then, new information on pathophysiology of neonatal seizures and data on the safety and efficacy of treatment options have been released

II. **WHO guidelines on neonatal seizures**
   a. Decision to start antiepileptic drugs (AEDs) is controversial
      i. Physicians who believe seizures can worsen neurological status will treat even subclinical seizures while others will not
   b. Treatment of underlying etiologies if possible
      i. To determine etiologies:
         1. Cranial ultrasound
         2. MRI
         3. CAT scans
      ii. Etiologies and treatments:
         1. Sepsis – empiric antibiotics + antivirals
         2. Meningitis – empiric antibiotics + antivirals
         3. Hypoglycemia – supplement glucose
         4. Hypocalcaemia – supplement calcium
         5. Hypomagnesemia – supplement magnesium
         6. Vitamin B6 deficiency – supplement vitamin B6 (pyridoxine)
   c. First line
      i. First-generation AEDs: first line because of extensive clinical experience, despite limited effectiveness
      ii. Agent: phenobarbital
   d. Second line
      i. Second-generation AEDs: data are scarce and efficacy and safety have yet to be established in the neonatal population
      ii. Agents: phenytoin, benzodiazepines (ex: midazolam, lorazepam), lidocaine
   e. Additional agents since WHO guidelines
      i. As more information became available, additions to the WHO algorithm have been proposed in different case reports and studies
      ii. Agents introduced as second or third line: levetiracetam (LEV), topiramate, and bumetanide
   f. Successful treatment
      i. If the EEG is normal, treatment may be stopped if the neonate has been seizure-free for greater than 72 hours
      ii. Drug(s) should be reinstituted in cases of recurrence of seizures
      iii. Tapering of drugs:
         1. Monotherapy – tapering is unnecessary
         2. Dual therapy – drugs should be removed one-by-one
Figure 3. 2011 World Health Organization (WHO) guidelines for neonatal seizures⁵ [Appendix D]

When to treat:

- Clinically apparent seizures lasting > 3 minutes

Rule out other etiologies:

- Check for and resolve if present: hypoglycemia, sepsis, meningitis, hypocalcaemia, hypomagnesemia

1st line:

- Phenobarbital

2nd line: (for refractory seizures)

- Phenytoin
- Benzodiazepines (ex: midazolam, lorazepam)
- Lidocaine

Phenobarbital

I. Current place in therapy⁷-⁸
   a. Standard first line agent recommended in guidelines and utilized in clinical practice

II. Mechanism of action
   a. Exhibits gamma-aminobutyric acid (GABA)-like effects similar to benzodiazepines and reversibly depresses activity of all excitable tissue
   b. Produces degrees of CNS depression and respiratory depression at higher doses

III. Safety
   a. Acute
      i. CNS and respiratory depression
      ii. Behavioral changes (hyperactivity)
      iii. Depressed mood/affect
   b. AEDs and apoptosis in the developing brain (2003)⁹
      i. Phenobarbital 30-75 mg/kg
      ii. Black column: apoptotic scores in saline treated rats (Co)
      iii. Neuronal apoptosis at concentrations of 25-35 mcg/mL
         1. Within therapeutic window of 15-40 mcg/mL
      iv. Thick line at the bottom indicated the effective dose that blocks seizures in 50% of rats (ED₅₀) of the corresponding drug in various drug seizure models
Figure 4. Degree of neuronal degradation with phenobarbital use in 7-day old rats

Figure 5. Efficacy of phenobarbital

Levetiracetam

I. Current place in therapy
   a. Not currently listed as a therapeutic option in guidelines
   b. 2012 – approved by Food and Drug Administration (FDA) for use in patients one month of age and older

II. Mechanism – exact mechanism unknown
   a. Inhibition of voltage-dependent N-type calcium channels
   b. Facilitation of GABA-ergic inhibitory transmission through displacement of negative modulators
   c. Reduction of delayed rectifier potassium current
   d. Binding to synaptic proteins which modulate neurotransmitter release

III. Safety
   a. Acute:
      i. Irritability/agitation
      ii. Lethargy
      iii. Insomnia
b. The effect of LEV on neuronal apoptosis in neonatal rat model of hypoxic ischemic brain injury (2012)\textsuperscript{10}
   i. There were 3 groups of 7-day old rat pups analyzed
      1. Saline (placebo) group: subjected to right common carotid artery ligation and hypoxia for 2 hours and treated with saline
      2. LEV (treatment) group: subjected to right common carotid artery ligation and hypoxia for 2 hours and treated with LEV
      3. “Sham” group: neither ligation nor hypoxia was performed

   \begin{figure}[h]
   \centering
   \includegraphics[width=0.5\textwidth]{apoptotic_cells.png}
   \caption{Apoptotic cells in the cerebral cortex and hippocampus of the sham, saline, and LEV treated groups\textsuperscript{10}}
   \end{figure}

   ii. Counts of apoptotic cells in the hippocampus and cerebral cortices of the pups in the saline group were higher than those in the LEV group (p<0.0006)
   iii. LEV administration after hypoxia reduces neuronal apoptosis

IV. Efficacy\textsuperscript{12}
   a. Not well defined due to lack of prospective clinical trials and availability of data with LEV as initial therapy and/or monotherapy

Clinical Question

Should LEV be moved up in the algorithm for treatment of neonatal seizures to be utilized before the long-standing first line agent phenobarbital?

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To compare neurodevelopment after LEV and phenobarbital for neonatal seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective cohort study</td>
</tr>
</tbody>
</table>

**Patient Population**

*Inclusion:*
- Had at least one observed clinical seizure
- Received phenobarbital or LEV for a diagnosis of seizures, as documented on the electronic medical record

*Exclusion:*
- Patients born at another facility who had already received either phenobarbital or LEV prior to admission
- Seizure occurred more than 48 hours before transfer to study facility
- If antiepileptic drug administration data at the referring hospital were unavailable

**Outcomes**

- Death within the first two years of age
- Neurodevelopmental outcomes as measured by motor, cognitive, and language performance on the Developmental Assessment of Young Children (DAYC) at 12 months and the Bayley Scales of Infant Development (BSID) 3rd edition at 24 months
- Identify children with a diagnosis of cerebral palsy (CP) by two years of age, made by pediatric specialists according to published criteria and scored for severity using the Gross Motor Function Classification System (GMFCS)

**Methods**

- Varied and inconsistent practices
- Phenobarbital was the only antiepileptic used by neonatal transport teams across Tennessee (TN) at the time of study
- Patients started on LEV as first line were immediately referred to a pediatric neurologist and started per their recommendation

**Statistics**

- Categorical variables were summarized using percentages
- Linear regression models to determine the correlation of DAYC and BSID scores to exposure to phenobarbital and LEV while controlling for confounding variables
- Logistic regression was used to estimate the association of CP with phenobarbital or LEV exposure while controlling for gestation age and severity of seizure disorder
- Dose-response relationship: expected change in DAYC and BSID scores reported as scores per 100 mg/kg increase in phenobarbital and 300 mg/kg increase in LEV, representing approximately one third of the range of cumulative doses for each of the drugs

**Results**

- N = 280 patients
  - ONLY phenobarbital: 106 patients
  - ONLY LEV: 33 patients
  - Both phenobarbital and LEV: 144 patients
  - Cumulative exposure
    - ANY phenobarbital: 247 patients
    - ANY LEV: 174 patients
    - Overlap: 141 patients
- No significant differences between groups at baseline regarding sex, race/ethnicity, maternal education level, seizure etiology, seizure severity (determined by the number of electrographic seizures), or number of observed clinical seizures
- Increasing cumulative phenobarbital but not LEV exposure is associated with increased probability of CP. Shaded area represents 95% confidence interval (P < 0.025)
- Probability of developing CP was increased by 2.3-fold for every 100 mg/kg increase in phenobarbital
### Results

- **Follow-up data**
  - **24 months:**
    - **Phenobarbital:**
      - Decreasing cognitive score (BSID decreased by 8 points) \((P = 0.01)\) for every 100 mg/kg of phenobarbital exposure
      - Decreasing motor score (BSID decreased by 9 points) \((P = 0.023)\) for every 100 mg/kg of phenobarbital exposure
    - **LEV**
      - Decreasing cognitive score (BSID decreased by 2.2 points) \((P = 0.001)\) for every 300 mg/kg of LEV exposure
      - Decreasing motor score (BSID decreased by 2.6 points) \((P = 0.001)\) for every 300 mg/kg of LEV exposure

### Conclusions

- Increasing exposure to phenobarbital is associated with worse outcomes at two years of age
- LEV may be associated with improved outcomes compared with phenobarbital

### Critique

| **Strengths** | Large sample size for study of this nature  
|              | Long-term outcomes (up to two years of age)  
|              | DAYC and BSID provided standardized method for assessment of patient development |

| **Limitations** | Retrospective study  
|                 | Few infants only received one antiepileptic drug (ONLY phenobarbital or ONLY LEV)  
|                 | Patients with neonatal seizures are often followed by neurologists and developmental specialists rather than NICU follow-up clinic and their outcomes were unavailable for analysis in this study  
|                 | Test scores available for only two thirds at 12 months and one third at 24 months  
|                 | Only two thirds had CP assessments at 24 months |

| Purpose | • To evaluate the anticonvulsant efficacy and treatment safety of LEV in neonates with electroclinical and electrographic-only seizures |
| Design | • Prospective feasibility study |
| Patient Population | **Inclusion:**  
  • Newborns (both term and pre-term) admitted with EEG confirmed seizures  
**Exclusion:**  
  • Known major neurologic diseases and/or syndromes  
  • Neurologic symptoms due to metabolic causes (ex: hypoglycemia, hypocalcemia) |
| Outcomes | **Primary Outcome:** Evaluate the control of seizures, both clinically and electroencephalographically  
**Secondary Outcome:** Evaluate adverse effects associated with IV or PO administration of LEV |
| Methods | • Neonatal seizures defined as subtle, focal clonic, multifocal clonic, focal tonic, generalized tonic, and myoclonic  
  o Those with subtle presentation characteristics (ex: apneic spells), were a diagnostic challenge  
  • EEGs were performed at bedside in the NICU  
  • Protocol observed  
  o LEV dosing:  
    • Initial: 10 mg/kg twice daily  
    • Increased to 30 mg/kg/dose over 3 days  
    • Max dosing of 60 mg/kg/dose  
    • Switched to oral solution as soon as infants could tolerate PO administration  
  o IV phenobarbital considered as adjunctive therapy in cases resistant to LEV  
    • Two single IV doses of 20 mg/kg  
    • Tolerated during LEV titration to treat seizures that were prolonged or recurrent  
      • Duration over 5 minutes or over 2 episodes in 15 min  
  • Evaluated over 12 months |
| Statistics | • Percentages were used for data reporting  
  • Sample size limits the statistical analysis |
| Results | • N = 38 | **Table 2a. Baseline characteristics** |
| | | <28 weeks | 28-36 weeks | ≥37 weeks |
| Number of patients | 19 | 6 | 13 |
| Age at seizure onset < 48 hours | - | 3 (50%) | 8 (62%) |
| Age at seizure onset > 48 hours | 19 (100%) | 3 (50%) | 5 (38%) |
| Neurologic status | | | |
| Normal | 8 (42%) | - | - |
| Mildly abnormal | 4 (21%) | 1 (17%) | 2 (15%) |
| Moderately abnormal | 5 (26%) | 4 (67%) | 9 (69%) |
| Severely abnormal | 2 (11%) | 1 (17%) | 2 (15%) |
Table 2b. Resolution of seizures

<table>
<thead>
<tr>
<th></th>
<th>&lt;28 weeks (n = 14)</th>
<th>28-36 weeks (n = 4)</th>
<th>≥37 weeks (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adj PB</td>
<td>No PB</td>
<td>Adj PB</td>
</tr>
<tr>
<td>Seizure free at 7 days</td>
<td>3 (21%)</td>
<td>11 (79%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Seizure recurrence</td>
<td>1 (7%)</td>
<td>0</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Seizure free at 30 days</td>
<td>1 (5%)</td>
<td>10 (71%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Seizure recurrence</td>
<td>0</td>
<td>1 (5%)</td>
<td>1 (25%)</td>
</tr>
</tbody>
</table>

Adj = adjunctive; PB = phenobarbital

Results

- Seizure free (N = 38)
  - 30 infants by the end of week 1
  - 27 infants by the end of week 4
- Improvement in EEG
  - 25 infants at week 4
- Outcomes at 6 and 12 months

Table 2c. Follow-up data

<table>
<thead>
<tr>
<th></th>
<th>&lt;28 weeks</th>
<th>28-36 weeks</th>
<th>≥37 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>11</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Mortality</td>
<td>-</td>
<td>1 (17%)</td>
<td>-</td>
</tr>
</tbody>
</table>

6 months

- Post-neonatal epilepsy | 3 (27%) | 1 (33%) | 2 (17%) |
- Developmental delay | 6 (55%) | 1 (33%) | 5 (42%) |
- Co-morbidity | 5 (45%) | - | 1 (8%) |

12 months

- Post-neonatal epilepsy | 3 (27%) | - | 2 (17%) |
- Developmental delay | 5 (45%) | - | 3 (25%) |
- Co-morbidity | 4 (36%) | - | - |

- No severe adverse effects of LEV were observed

Conclusions

- LEV is safe and efficacious in neonates for the treatment of neonatal seizures
- Larger, prospective, randomized trials should be conducted to confirm these results

Critique

Strengths

- LEV utilized as first line agent without confounding prior anticonvulsant use
- Prospective data collection
- Year-long follow-up provides information previously unknown for LEV use in neonates

Limitations

- Small sample size
- Non-randomized
- Simultaneous video-EEG monitoring was not performed

| Purpose | To evaluate the efficacy and safety of LEV as first-line treatment of neonatal seizures |
| Design | Prospective observational study |

**Patient Population**

**Inclusion:**
- Preterm and term neonates with signs and/or symptoms of neonatal seizures and/or HIE

**Exclusion:**
- Known major neurologic diseases and/or syndromes
- Neurologic symptoms due to metabolic causes (ex: hypoglycemia, hypocalcemia)
- Those with major cardiovascular and surgery diseases
- Known hypersensitivity to drugs

**Outcomes**

**Primary & Secondary Outcomes:** Not explicitly stated in article
- Resolution of baseline pathologic EEGs, resolution of baseline cerebral ultrasounds, time to resolution, requirement of adjacent phenobarbital therapy

**Methods**

- Protocol observed
  - IV LEV dosed as:
    - Initial: 10 mg/kg twice daily
    - Dose titration occurred every 24 hours
    - Gradually increase doses up to 40 mg/kg twice daily in case of nonresponse to lower doses
  - IV phenobarbital considered as adjunctive therapy in cases resistant to LEV

**Statistics**

- Qualitative variables expressed as percentages
- Quantitative variables expressed as mean ± standard deviation
- Tested approximation to normal of the distribution of the population by using Kolmogorov-Smirnov One-Sample Test and statistics for kurtosis and symmetry

**Results**

**N = 16**

<table>
<thead>
<tr>
<th>Table 3a. Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean weight</strong></td>
</tr>
<tr>
<td><strong>Mean head circumference</strong></td>
</tr>
</tbody>
</table>

**Perinatal history**

| Meconium aspiration syndrome | 5 (31.2%) |
| Respiratory distress         | 8 (50%)   |
| Fetal blood circulation disease | 2 (12.5%) |
| Acute placental detachment   | 3 (18.75%)|
| Generalized hypotonia (axial) | 16 (100%) |
| Generalized hypotonia (peripheral) | 16 (100%) |

**Mean APGAR**

| 1st min | 5.12 (± 3.70 SD) |
| 5th min | 6.87 (± 3.20 SD) |
| Mean onset of symptoms | 3.3 ± 1.2 days after birth |
Table 3b. Follow-Up Data

Results

<table>
<thead>
<tr>
<th>After 3 months of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pathologic EEGs were normal when referred to gestational age</td>
</tr>
<tr>
<td>Cerebral ultrasounds showing presence of hemorrhage was reabsorbed at T2</td>
</tr>
<tr>
<td>All patients responded to treatment, with a variety range of seizure resolution period</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours to 15 days</td>
</tr>
<tr>
<td>(mean: 96 hours ± 110.95 hours)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients requiring a second anticonvulsant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Routine blood tests normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (87.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mild hypertransaminasemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (12.5%)</td>
</tr>
</tbody>
</table>

Conclusions

- LEV was efficient in resolving seizures and did not require adjunctive therapy
- LEV was well-tolerated overall with some mild hypertransaminasemia (resolved upon adjusting dose of LEV)
- Larger multicenter clinical trial needed to design guidelines on the use of LEV in neonatal seizures

Critique

Strengths

- Prospective data collection
- LEV used as first line monotherapy
- Population included both term and pre-term neonates

Limitations

- Small sample size
- Observational study
- Follow-up longer than 6 months not available
- Average doses of effect were not reported
- Severity of hypertransaminasemia not reported for reader’s clinical interpretation
Summary

I. Phenobarbital
   a. Pros
      i. Newborn pharmacokinetic (PK) data are better known for phenobarbital than other medications
      ii. Available in both IV and PO formulations
      iii. Affordable and readily-available world-wide
   b. Cons
      i. Therapeutic drug monitoring required
         1. Reference range: 10-40 mg/L
      ii. Short-term: risk of CNS and respiratory depression
      iii. Long-term: poor neurodevelopmental outcomes

II. LEV
   a. Pros
      i. Favorable PK profile
      ii. Monitoring (available for resistant cases) is not required because of large therapeutic window and minimal side effect profile
   b. Cons
      i. Unknown mechanism of action
      ii. Lack of significant prospective studies
      iii. In many available studies, LEV is not used as a first-line agent or as monotherapy

Current trends in antiepileptic drug utilization

I. Changing AED use for seizures in US neonatal intensive care units from 2005-2014
   a. Phenobarbital is still the #1 most utilized anticonvulsant for neonatal seizures
   b. 2005-2006 to 2013-2014
      i. Phenobarbital exposure has declined from 99% to 96% (P < 0.001)
      ii. LEV exposure has increased 10-fold from 1.4% to 14% (P < 0.001)

Treatment recommendations

• Rule out other etiologies (infections, metabolic abnormalities, vitamin deficiencies) and treat accordingly
• First line: LEV
  o LEV dosing:
    ▪ Initial: 10 mg/kg twice daily
    ▪ Increased to 30 mg/kg/dose over 3 days
    ▪ Max dosing of 60 mg/kg/dose
    ▪ Switch to oral solution as soon as infants can tolerate PO administration
• Second line: adjunctive phenobarbital
  o IV phenobarbital considered as adjunctive therapy in cases resistant to LEV
    ▪ Two single IV doses of 20 mg/kg
    ▪ Tolerated during LEV titration to treat seizures that were prolonged or recurrent
      • Duration over 5 minutes or over 2 episodes in 15 minutes
• If still no resolution, follow established WHO algorithm
References:

Appendix A. Pre-/post-inhibitory neurons in neonatal and mature brains with mechanisms of common AEDs (including benzodiazepines and barbiturates) ¹

GABA – gamma-Aminobutyric acid; Na – sodium; K – Potassium; Cl – chloride

Appendix B. Differential diagnosis of neonatal seizures²

<table>
<thead>
<tr>
<th>Cause of Etiology</th>
<th>Differential Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal asphyxia</td>
<td>HIE</td>
</tr>
<tr>
<td></td>
<td>Intraventricular hemorrhage</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Traumatic</td>
</tr>
<tr>
<td></td>
<td>With infarction</td>
</tr>
<tr>
<td>Infectious disorders</td>
<td>Intrauterine (cytomegalovirus, rubella, toxoplasmosis)</td>
</tr>
<tr>
<td></td>
<td>Prenatal (bacterial meningitis, herpes simplex, sepsis)</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Fructose dysmetabolism</td>
</tr>
<tr>
<td></td>
<td>Glycogen synthase deficiency</td>
</tr>
<tr>
<td></td>
<td>Urea cycle-disorders</td>
</tr>
<tr>
<td></td>
<td>Glycine encephalopathy</td>
</tr>
<tr>
<td>Cerebral dysgenesis</td>
<td></td>
</tr>
<tr>
<td>Bilirubin encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Intoxication</td>
</tr>
<tr>
<td></td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Other genetic defects</td>
<td>Benign familial neonatal seizures</td>
</tr>
<tr>
<td></td>
<td>Pyridoxine dependency</td>
</tr>
<tr>
<td></td>
<td>Incontinentia pigmenti</td>
</tr>
</tbody>
</table>
### Appendix C. Differential diagnosis of neonatal seizures by peak time of onset

<table>
<thead>
<tr>
<th>24 hours</th>
<th>24 hours to 72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIE</td>
<td>Bacterial meningitis and sepsis</td>
</tr>
<tr>
<td>Bacterial meningitis and sepsis</td>
<td>Cerebral contusion with subdural hemorrhage</td>
</tr>
<tr>
<td>Direct drug effects</td>
<td>Cerebral infarction</td>
</tr>
<tr>
<td>Intrauterine infection</td>
<td>Drug withdrawal</td>
</tr>
<tr>
<td>Intraventricular hemorrhage at term</td>
<td>Intracerebral hemorrhage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>72 hours to 1 week</th>
<th>1 week to 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial neonatal seizures</td>
<td>Fructose dysmetabolism</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>Gaucher disease type 2</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Herpes simplex encephalitis</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>Kernicterus</td>
<td>Cerebral dysgenesis</td>
</tr>
</tbody>
</table>

### Appendix D. Drugs used for the treatment of neonatal seizures

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Side Effects</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Long-acting barbiturate that depresses the sensory cortex and motor activity</td>
<td>Loading dose: 15-20 mg/kg Maintenance dose: 3-4 mg/kg once daily starting 12-24 hours after loading dose</td>
<td>CNS depression Respiratory depression Agitation Neuronal apoptosis</td>
<td>Available as both IV and PO Efficacy: controls seizures in 43-63% of newborns</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Precise mechanism unknown</td>
<td>Initial: 10 mg/kg/day divided twice daily increased by 10 mg/kg over 3 days to 30 mg/kg/day</td>
<td>Agitation Lethargy Insomnia</td>
<td>Available as both IV and PO</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Stabilizes neuronal membranes by increasing efflux or decreasing influx of sodium ions across cell membranes in the motor cortex</td>
<td>Loading dose: 15-20 mg/kg Maintenance dose: 5 mg/kg/day in two divided doses</td>
<td>CNS depression Hypotension Neuronal apoptosis</td>
<td>Efficacy: controls seizures in up to 45% of newborns Poor bioavailability (IV preferred)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Binds to stereospecific benzodiazepine receptors on the post-synaptic GABA neuron at several sites within the CNS enhancing inhibitory effect</td>
<td>Loading dose: 0.06-0.15 mg/kg/dose Continuous infusion: 0.06-0.4 mg/kg/hour</td>
<td>CNS depression Respiratory depression Hypotension Possible apoptosis</td>
<td>Very limited clinical data Efficacy unknown; utilized as second or third line agent</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane’s permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction</td>
<td>Loading dose: 2 mg/kg over 10 min followed by a weight-based continuous infusion</td>
<td>Risk of arrhythmias (especially with cardiac dysfunction or hyperkalemia)</td>
<td>No longer commonly used in modern clinical practice Dosing varies based on if the patient is receiving therapeutic hypothermia</td>
</tr>
</tbody>
</table>
Appendix D [continued]. Drugs used for the treatment of neonatal seizures

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Side Effects</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topiramate</strong></td>
<td>Potentially several mechanisms; blocking sodium channels, enhancing GABA activity, antagonizing glutamate receptors, weak inhibition of carbonic anhydrase</td>
<td>10 mg/kg/day</td>
<td>Anorexia, Metabolic acidosis, Lethargy, Irritability</td>
<td>Very limited human data but promising animal data, Oral, immediate release formulation</td>
</tr>
<tr>
<td><strong>Bumetanaide</strong></td>
<td>Inhibits reabsorption of sodium and chloride in the ascending loop of Henle and proximal renal tubule causing increased excretion of water, sodium, chloride, magnesium, phosphate, and calcium</td>
<td>[None listed for treatment of seizures]</td>
<td>Fluid/electrolyte imbalance, Hemodynamic instability, Ototoxicity</td>
<td>Promising experimental data</td>
</tr>
</tbody>
</table>