Seizures in the Neonate: Acute Symptomatic Seizures and Early Onset Epilepsy

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Objectives

✓ Describe the most common causes of seizures in newborns
✓ Understand the difference between acute symptomatic seizures and epilepsy
✓ Know the evidence for and current limitations of medical management of neonatal seizures
✓ Develop a local treatment strategy for neonatal seizures
Neonates

1-4/1000 live births
Seizures Often Reflect Injury

1° causes of seizures (~70%)

Glass HC et al, J Pediatr, 2016
... and Adverse Outcome

125 with acute symptomatic neonatal sz

- Neonatal Death 26%
- Cerebral Palsy 21%
- Epilepsy 9%
- Bayley Cognitive Subscale <85 13%

Glass HC et al, Pediatric Neurology, 2018
Seizure Types

• Clinical only
  – No EEG correlate

• Electrical only
  – EEG only, no clinical correlate

• Electroclinical
  – EEG and clinical
What is the Best Medication?

“…little evidence from randomized controlled trials to support the use of any of the anticonvulsants currently used in the neonatal period.”

Booth D and Evans DJ, Cochrane Database Syst Rev 2004
What do MDs Use?

Survey says...

Bartha AI et al, Ped Neurol 2007
Wheless JW et al, Epileptic Disord 2007
Bassan et al, Ped Neurol 2008
Table III. Seizure management among 426 neonates with clinically suspected and/or EEG confirmed seizures who were monitored by cEEG

<table>
<thead>
<tr>
<th></th>
<th>Overall, n = 426</th>
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<td><strong>Initial loading medication and dose</strong></td>
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<td>Phenobarbital (20 mg/kg, IQR 20, 20 mg/kg)</td>
<td>379 (89%)</td>
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<td>Levetiracetam (20 mg/kg, IQR 20, 32 mg/kg)</td>
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<td>4 (1%)</td>
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Glass HC et al, J Pediatr, 2016
# Phenobarbital

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<th>Pros</th>
<th>Cons</th>
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<tr>
<td>✓ It works ~50% of the time</td>
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<tr>
<td>✓ Pharmacokinetics, side effects and safety profile well understood</td>
<td>✗ Harmful to animals</td>
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<tr>
<td>✓ Readily available</td>
<td>✗ May be harmful to humans with prolonged use</td>
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<tr>
<td>✓ IV formulation available</td>
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<td>✓ Physician/RN/pharmacist comfort</td>
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### Table III. Seizure management among 426 neonates with clinically suspected and/or EEG confirmed seizures who were monitored by cEEG

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Levetiracetam

- Not harmful in animal models
- Good safety profile
- PK established
- Widely used in older children and adults

NEOLEV2 Trial: Protocol

Slide courtesy of Richard Haas and Cia Sharpe
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<tr>
<th>Outcome Description</th>
<th>LEV 40-60 mg/kg</th>
<th>PHB 20-40 mg/kg</th>
<th>Odds Ratio (95%CI)</th>
<th>p-value</th>
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<td><strong>Primary Outcome</strong></td>
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<td>24-hour seizure cessation rate (n=83)</td>
<td>15/53 (28%)</td>
<td>24/30 (80%)</td>
<td>9.8 (3.1-35.5)</td>
<td>&lt;0.001</td>
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<td><strong>Secondary Outcomes</strong></td>
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<td>48-hour seizure cessation rate (n=75)</td>
<td>8/47 (17%)</td>
<td>18/28 (64%)</td>
<td>8.5 (2.6-30.1)</td>
<td>&lt;0.001</td>
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<td>1-hour seizure cessation rate (n=83)</td>
<td>26/53 (49%)</td>
<td>28/30 (93%)</td>
<td>14.1 (3.1-134.6)</td>
<td>&lt;0.001</td>
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<td><strong>Subjects with HIE treated with hypothermia</strong></td>
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<td>24-hour seizure cessation rate (n=27)</td>
<td>6/17 (35%)</td>
<td>9/10 (90%)</td>
<td>14.6 (1.5-7.8)</td>
<td>0.014</td>
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*Phenobarbital superior: intent to treat, per protocol, imputation analysis (p<0.001)

NB – Higher rate of hypotension with phenobarbital

Slide courtesy of Richard Haas and Cia Sharpe
Higher Efficacy of Pb in all Seizure Severity Groups

Pre-treatment Seizure Burden (sec/hr of the worst hour prior to treatment)

Slide courtesy of Richard Haas and Cia Sharpe
Phenobarb vs Phenytoin

Enrolled (n=59)

- Randomly assigned to phenobarbital (n=30)
  - Complete control achieved (n=13)
    - Phenytin administered (n=15)
      - Complete control achieved (n=4)
    - Therapy failed (n=17)
      - No phenytoin administered (n=2)
      - Therapy failed (n=11)
  
- Randomly assigned to phenytoin (n=29)
  - Complete control achieved (n=13)
    - Phenobarbital administered (n=13)
      - Complete control achieved (n=5)
    - Therapy failed (n=16)
      - No phenobarbital administered (n=3)

Phenobarb 43%
PHT 44%

Painter et al, NEJM 1999
Midazolam

• Midazolam bolus 0.2mg/kg IV
  – + infusion 0.1mg/kg/hr
  – Bolus 0.1-0.2mg/kg and titrate by 0.1mg/kg/hr prn

• Consider for status epilepticus
Developing a Treatment
Strategy: Acute Symptomatic

- Acute Symptomatic (HIE, stroke, hemorrhage, infection, etc) - 72%
- Epilepsy (epileptic encephalopathy eg KCNQ2, malformation, benign neonatal familial) - 14%
- Transient (hypoglycemia, hypocalcemia) - 4%
- Other/Unknown - 10%

Glass HC et al, J Pediatr, 2016
Response to Anti-Seizure Medication

534 Neonates at 9 sites: Overall incomplete response 66%

Similar Response
• Gestational ages
• Initial loading medication selection or dose

Intracranial hemorrhage (vs HIE or stroke)

Risks for Poor Response
• No therapeutic hypothermia (HIE)
• High seizure burden
• Abnormal initial EEG background

Be prepared to administer 2nd and 3rd line medications

Glass HC et al, Epilepsia 2019
Severe Seizures Are Harder to Treat

Treat seizures before they are “entrenched”
Early, rapid treatment is more likely to be effective

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<tr>
<th>Seizure Severity</th>
<th>Seizure Control</th>
<th>p-value</th>
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<tr>
<td>Mild</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>59%</td>
<td>0.05</td>
</tr>
<tr>
<td>Severe</td>
<td>1%</td>
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Acute Symptomatic Seizures: Usually Resolve <72 Hours

Lynch LE et al, Epilepsia 2012
No Harmful Effect of Early Discontinuation of Medication

- <10% recurrence despite short duration treatment
  
  Hellstrom-Westas et al, Arch Dis Childhood 1995; Glass HC et al Ped Neurol 2018

- No difference in recurrence if discharged home on phenobarbital vs no ASM
  - Non-randomized data
  
  Guillet and Kwon, Child Neurol 2007

- Variable treatment practice
  - Survey: MDs discontinue after resolution of acute seizures vs continue up to 6 months
  
  Kwon and Guillet, Pediatrics 2008

  - 7 site cohort study: Continuation 73% (range 4-91% by site)
  
  Shellhaas RA/Glass HC et al, J Peds 2017

Consider discontinuing meds before D/C
Is the patient at high risk for seizures?
- Encephalopathy
- Known brain injury
- Known EEG seizures
- Abnormal EEG background

**Use local medication guideline**
What to do When there is No Clear Acute Symptomatic Cause

• Red flags:
  – Seizures persist >4 days
  – MRI normal

• Next steps:
  – Go back to the history & physical examination for clues
  – Parents with “baby” seizures, on phenobarbital?
  – Fetal exposures?
  – Is the EEG normal or abnormal?
Strategy: Suspected Epilepsy

72% Acute Symptomatic (HIE, stroke, hemorrhage, infection, etc)

14% Epilepsy (epileptic encephalopathy eg KCNQ2, malformation, benign neonatal familial)

4% Transient (hypoglycemia, hypocalcemia)

10% Other/Unknown

Glass HC et al, J Pediatr, 2016
Early Onset Epilepsy: Genetic

- NSR: 68% of those tested had an identified genetic etiology
  - KCNQ2 mutations were most common
  - SCN2a mutation, SCN1a, SLC13A5, STXBP1, KCNT1, GDLC, CDKL5, CHD7, and TSC2

*High yield of genetic testing (infantile epilepsy gene panel)*
Benign vs Malignant

KCNQ2 Epilepsies

Benign Familial Neonatal Seizures

- Exam is normal
- Baby takes oral feeds
- Autosomal dominant

KCNQ2 Encephalopathy

- Exam is abnormal
- Baby needs NG feeds
- De novo mutation

Both respond to carbamazepine/oxcarbazepine
Early Onset Epilepsy: Brain Malformation

• Disorders of neuronal migration
  – 5 lissencephaly
  – 3 polymicrogyria
  – 3 focal cortical dysplasia
  – 2 schizencephaly (1 w/ polymicrogyria)
  – 1 pachygyria
  – 1 subependymal gray matter heterotopia

• Other
  – 5 Dandy-Walker malformations
  – 3 holoprosencephaly
  – 2 hemimegalencephaly
  – 1 septo-optic dysplasia

• 10 also had acute illness that predisposed to seizures
  – HIE, meningitis, glucose/electrolyte abnormalities.

Shellhaas RA et al Neurology. 2017
SSRIs and Neonatal Convulsions

- Early onset convulsions without EEG correlate
- Tremulousness
- Otherwise healthy neonate
- Management
  - EEG to confirm that events do not have an EEG correlate
  - Rule out brain injury and other causes of seizures

Supportive care
Vitamin Trial

Therapeutic Trials for Vitamin Responsive Epilepsies

• Pyridoxine 100 to 500 mg IV (continuous EEG monitoring recommended)
• Folinic acid 3-5 mg/kg/day enterally x 3-5 days
• PLP 30mg/kg/day enterally divided BID or QID x 3-5 days
Treatment Strategy

- Rapid and accurate seizure identification using neurophysiology monitoring
- Rapid implementation of medical therapy according to local guidelines
- Rapid titration to effect
- Rapid discontinuation of medication
- Consider the neonatal epilepsies when there is no clear cause especially if seizures are refractory
- Work with local medical team, mental health providers, and parent advocates to provide support
Newborn Brain Society

• Open Membership: $100US
• Free for trainees
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Children & Families