What's new in neonatal seizures and neonatal-onset epilepsy

Janet Soul, MDCM, FRCPC
Director, Fetal - Neonatal Neurology Program
Boston Children's Hospital
Associate Professor of Neurology
Harvard Medical School

Disclosures

- No personal financial disclosures or conflicts of interest to report related to this presentation
- I will discuss off label use of drugs (almost no antiseizure drugs approved for neonates)

Neonatal Seizures: Outline

1. Importance
2. Etiologies
3. Diagnosis
4. Management

Magnitude of the problem

- Seizures have highest incidence in newborns versus older children/adults
  - Incidence of 2-4/1000 live births
- Neonatal seizures associated with long-term neurologic disability
  - Epilepsy
  - Intellectual, motor and sensory disability
  - Robust animal data, some human data

Higher Seizure Severity associated with worse outcome

- Higher seizure burden associated with:
  - Greater mortality
  - Longer length of hospital stay
    - Glass,… Soul, J Peds 2016 Neonatal Seizure Registry
- Other studies also report worse outcome (e.g., CP) in HIE with higher seizure burden
    - e.g., McBride Neurol 2000, Kharoshankaya DMCN 2016

Chicken or egg?

- **Does more severe brain injury cause more severe seizures?**

OR

- **Do more severe seizures cause more severe brain injury?**

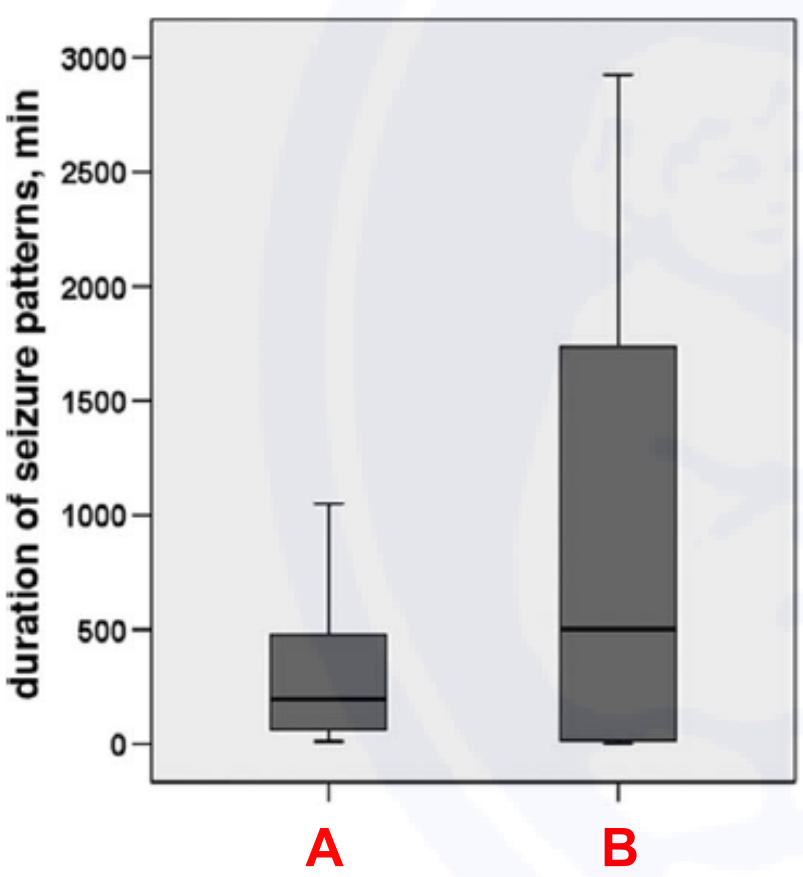
(or both?!!)

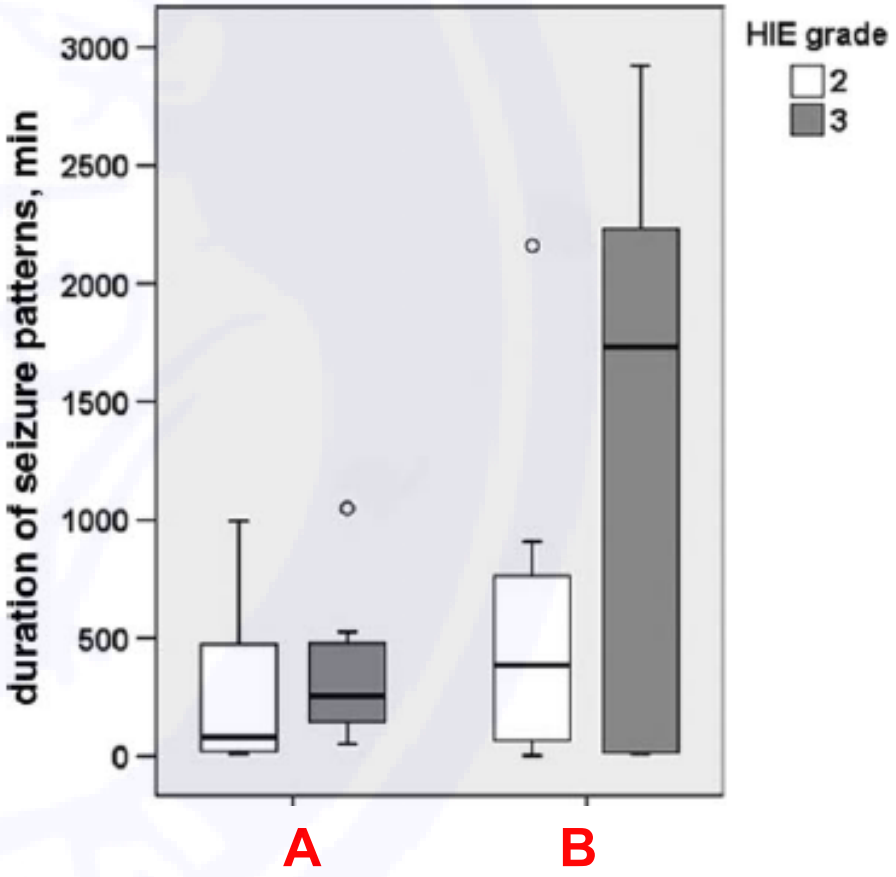
Two Trials of Electrographic vs. Clinical Seizure Treatment

- Newborns with HIE only
- Randomized treating clinical (CSG) vs. electrographic seizures (ESG)
  - One trial with aEEG (Europe)
    - Subjects: 19 CSG, 14 ESG
  - One trial with cvEEG (Washington Univ.)
    - Subjects: 20 CSG, 15 ESG

Van Rooij Peds 2010
Srinivasakumar Peds 2015

Trial of Electrographic (aEEG) vs. Clinical Seizure Treatment



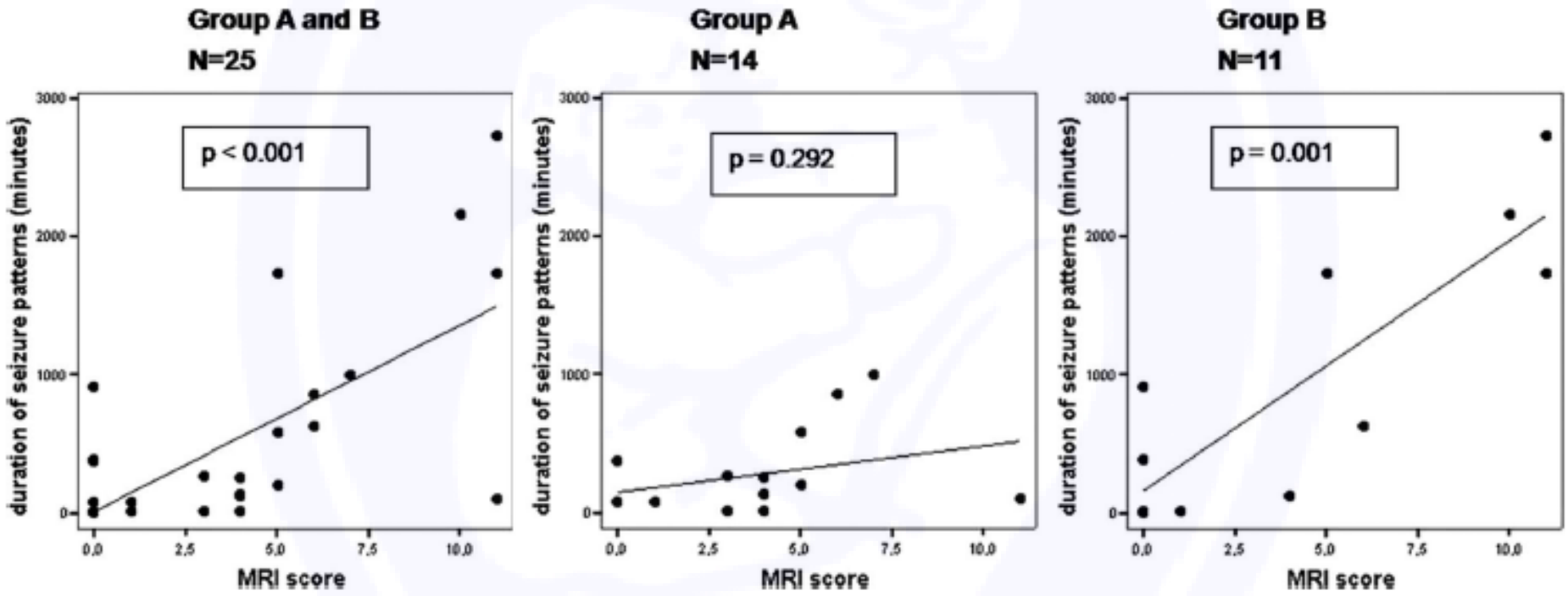


A = Treat aEEG-proven seizures

B = Treat only clinical seizures

Van Rooij Peds 2010

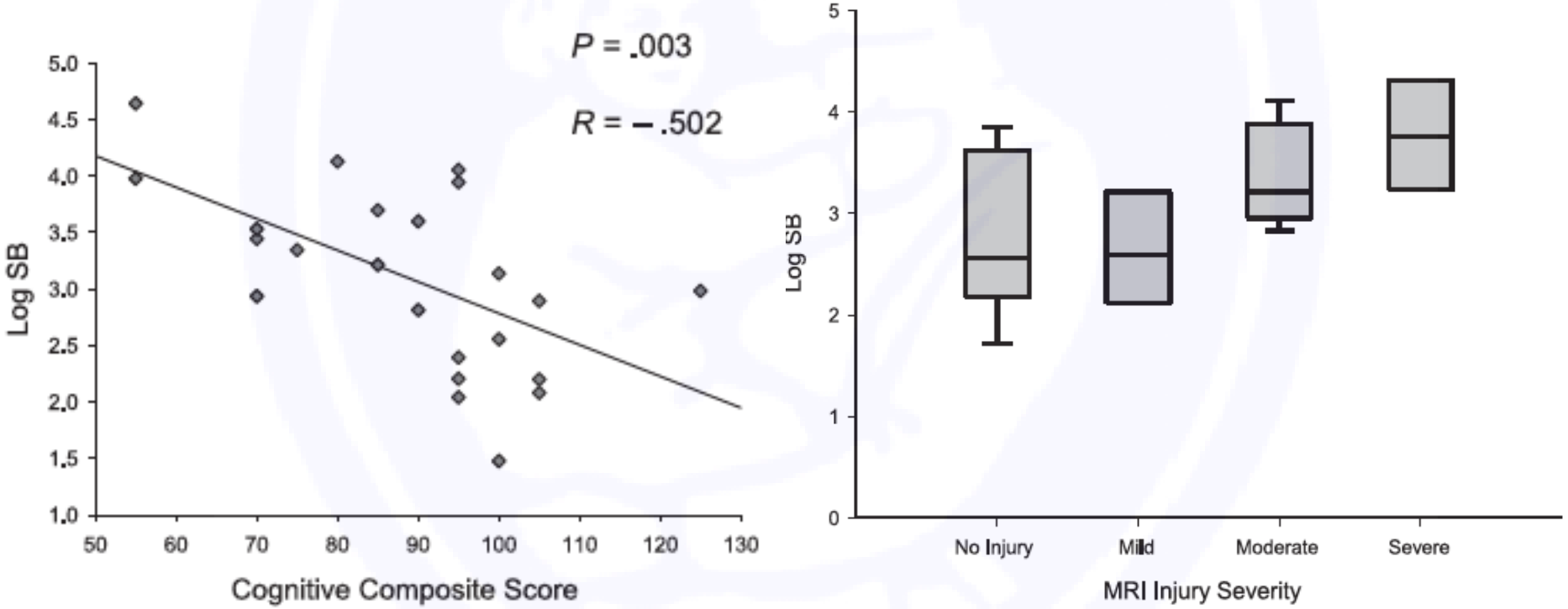
Trial of Electrographic (aEEG) vs. Clinical Seizure Treatment:
Association with brain injury by MRI



A = Rx subclinical szs
B= Rx clinical szs

Van Rooij Peds 2010

cvEEG trial: Higher seizure burden associated with worse outcome



Srinivasakumar Peds 2015

Two Trials of Electrographic vs. Clinical Seizure Treatment

- Fewer seizures and shorter seizure period with prompt treatment of EEG-proven seizures
- Hence:
  - Drugs are at least partially effective
  - Prompt treatment of EEG seizures might improve neurologic outcome

Van Rooij Peds 2010
Srinivasakumar Peds 2015

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Etiology of Neonatal Seizures

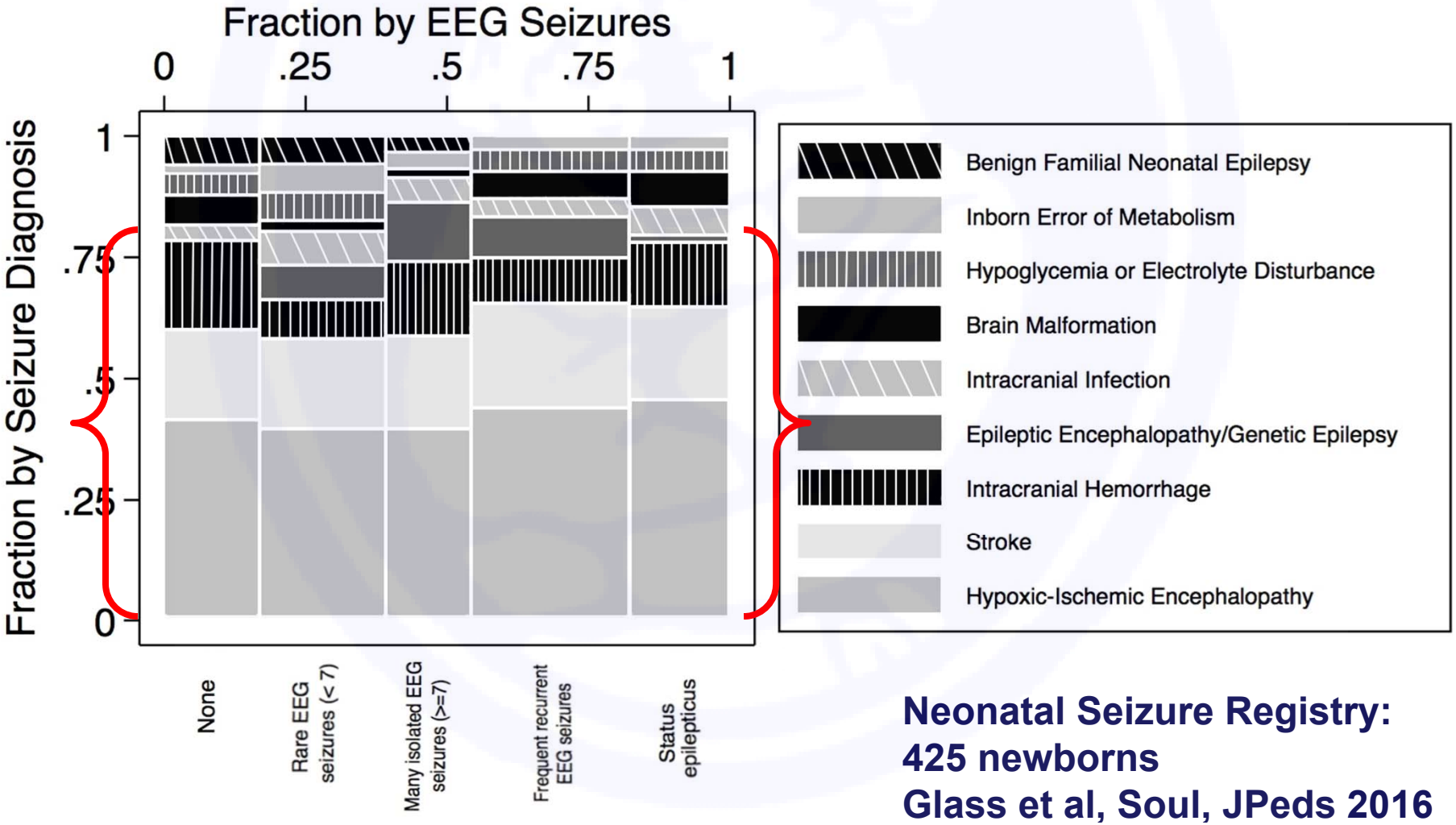
1. **Hypoxic-Ischemic Encephalopathy = HIE**
   - i.e., diffuse hypoxia-ischemia

2. **Stroke = arterial or venous infarction**
   - i.e., focal hypoxia-ischemia

3. **Intracranial Hemorrhage = ICH**
   - Intraventricular (IVH) ± thalamic venous stroke
   - Subdural +/- subarachnoid/subpial hemorrhage
   - Cerebral hemorrhage (parenchymal)

Distribution of seizure etiology and burden:

>75% from HIE, stroke, ICH
Seizure burden similar across etiologies



Neonatal Seizure Registry:
425 newborns
Glass et al, Soul, JPeds 2016

Etiology of Neonatal Seizures

4. Glucose and electrolyte abnormalities

- Hypoglycemia
- Hypocalcemia
- REMEMBER: electrolyte abnormalities may be caused by another underlying disorder
  - e.g., HIE, infection, metabolic / genetic disorder

Etiology of Neonatal Seizures

5. **Infection:**
   - **Meningitis / encephalitis**
     - **Bacterial: GBS, E. coli, Listeria**
     - **Viral: Herpes virus, parechovirus, enterovirus**
   - **Congenital / in utero infection:**
     - **CMV, Toxoplasmosis, Zika**

Etiology of Neonatal Seizures

5. **Brain malformation**
   - Holoprosencephaly, lissencephaly, polymicrogyria, focal cortical dysplasia, etc
6. **Genetic epilepsies**
   - benign neonatal epilepsy
     - e.g., KCNQ2/3 gene-related and others
   - neonatal epileptic encephalopathy
     - e.g., SCN1A, SCN2A, GABA receptor, CDKL5, and *many* others
7. **Metabolic disorders (genetic)**
   - Neurometabolic or systemic metabolic dx

Metabolic Disorders (genetic)

- Amino and organic acidemias
  - Including nonketotic hyperglycinemia
- Urea cycle defects
- Mitochondrial disorders
- Peroxisomal disorders, e.g., Zellweger
  - Polymicrogyria, other structural abnormalities
- Neurotransmitter related disorders
  - Pyridoxine, pyridoxal-5-phosphate, folinic acid
- Glucose transporter deficiency
  - Onset usually later in infancy

Neonatal Seizures: Outline

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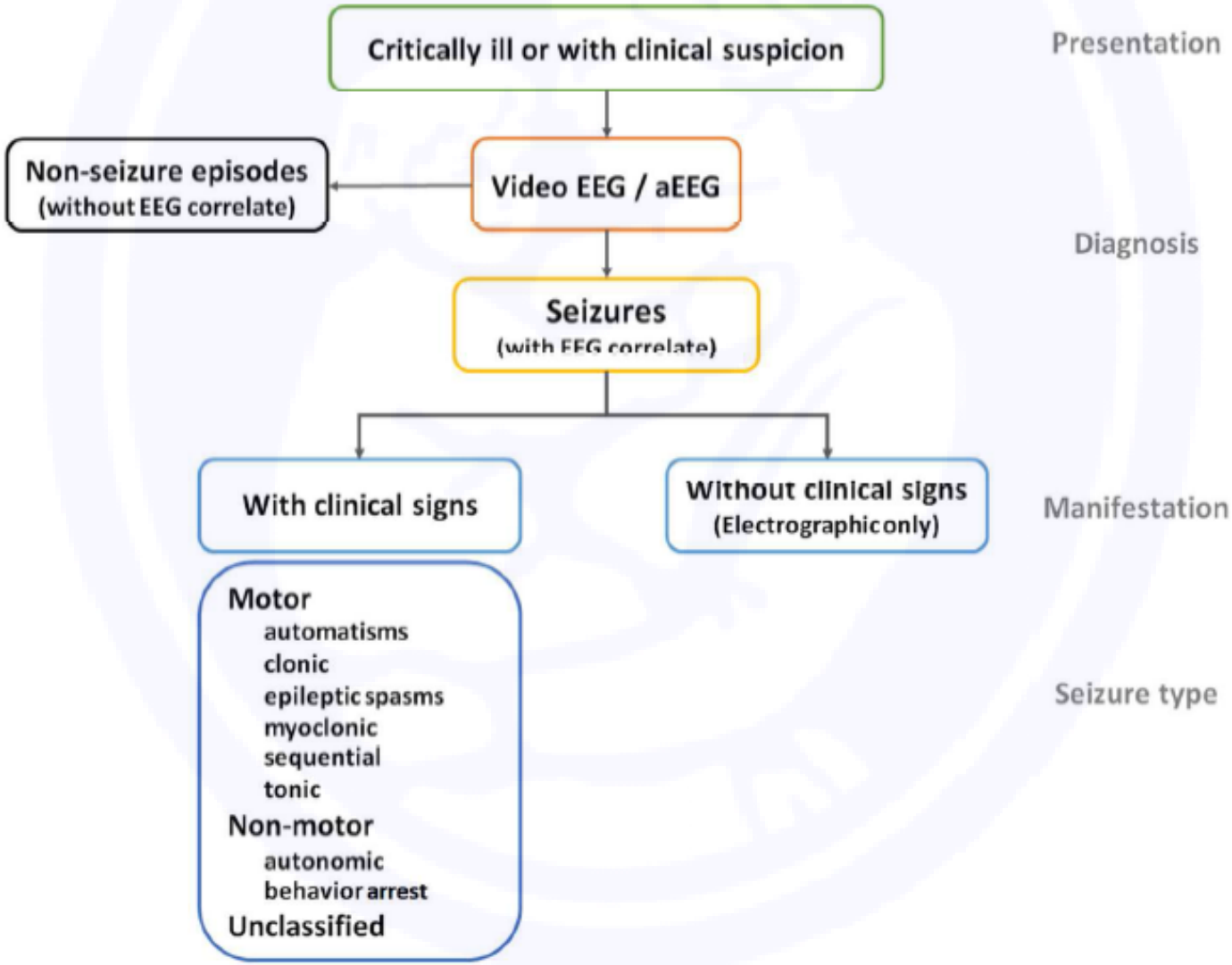
Proposed ILAE Classification of Neonatal Seizures (Draft)



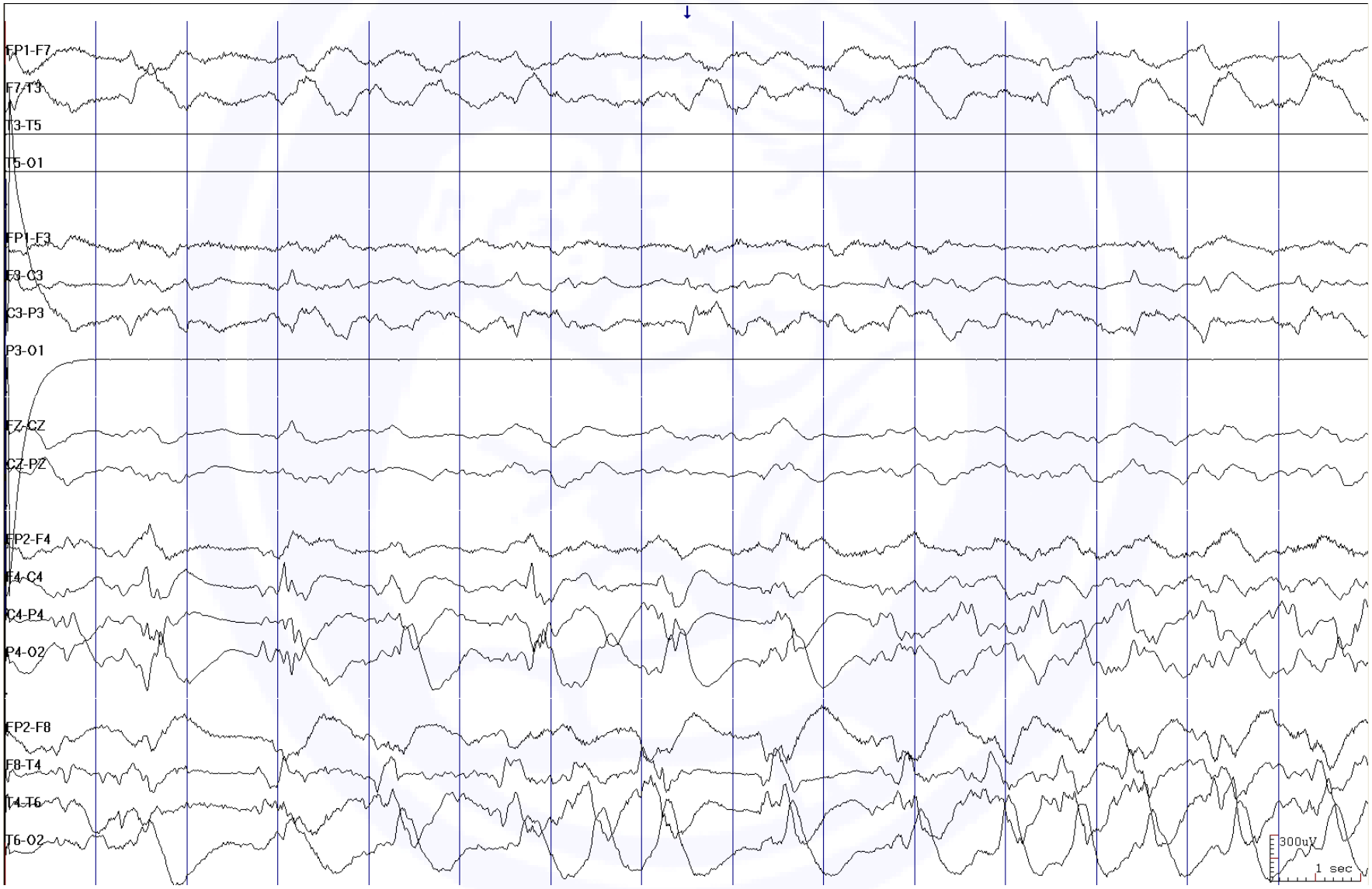
Seizure Type Suggests Etiology

- Focal unilateral clonic: stroke, focal ICH
- Multifocal and Myoclonic seizures: HIE, metabolic or genetic, e.g., epileptic encephalopathies (theme is diffuse brain disorder/dysfunction)
- Generalized tonic: often not seizure
  - e.g., can occur with severe IVH

Neonatal seizures: Diagnosis

- EEG is gold standard for diagnosis
  - Need continuous video-EEG monitoring (cvEEG)
- Since neonatal seizures are often:
  - subclinical (EEG only): >50% of seizures!!
    - 16% have only subclinical seizures
      - » Glass, Soul, J Peds 2016
  - subtle, brief, without vital sign changes
  - ➢ Easily missed, even with O2, cardiac monitors
- Frequent non-epileptic movements:
  - Tremors, jitteriness
  - Posturing, other behaviors
  - Myoclonus can be non-epileptic

Multifocal seizures from different regions



Neonatal Seizures: Outline

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What is the goal of neonatal seizure treatment?

Reduce seizure burden in order to:

1. Improve short-term outcome
2. Reduce long-term neurologic disability
3. Reduce risk of later epilepsy

Drugs to treat neonatal seizures

- **Limited efficacy & safety data**
  - **Few randomized, double-blind trials of antiseizure drugs**
  - **Several open label trials and retrospective studies**

Drugs to treat neonatal seizures

- Phenobarbital
- Phenytoin / fosphenytoin
- Levetiracetam
- Lidocaine
- Midazolam
- Others

One Published Randomized Drug Trial for Neonatal Seizures

- Phenobarbital vs. phenytoin as first line
  - Phenobarbital (PB) 43% effective
  - Phenytoin (PHT) 45% effective
  - PB + PHT combined 57% effective

Painter NEJM 1999

Phenobarbital vs. phenytoin trial

Painter NEJM 1999

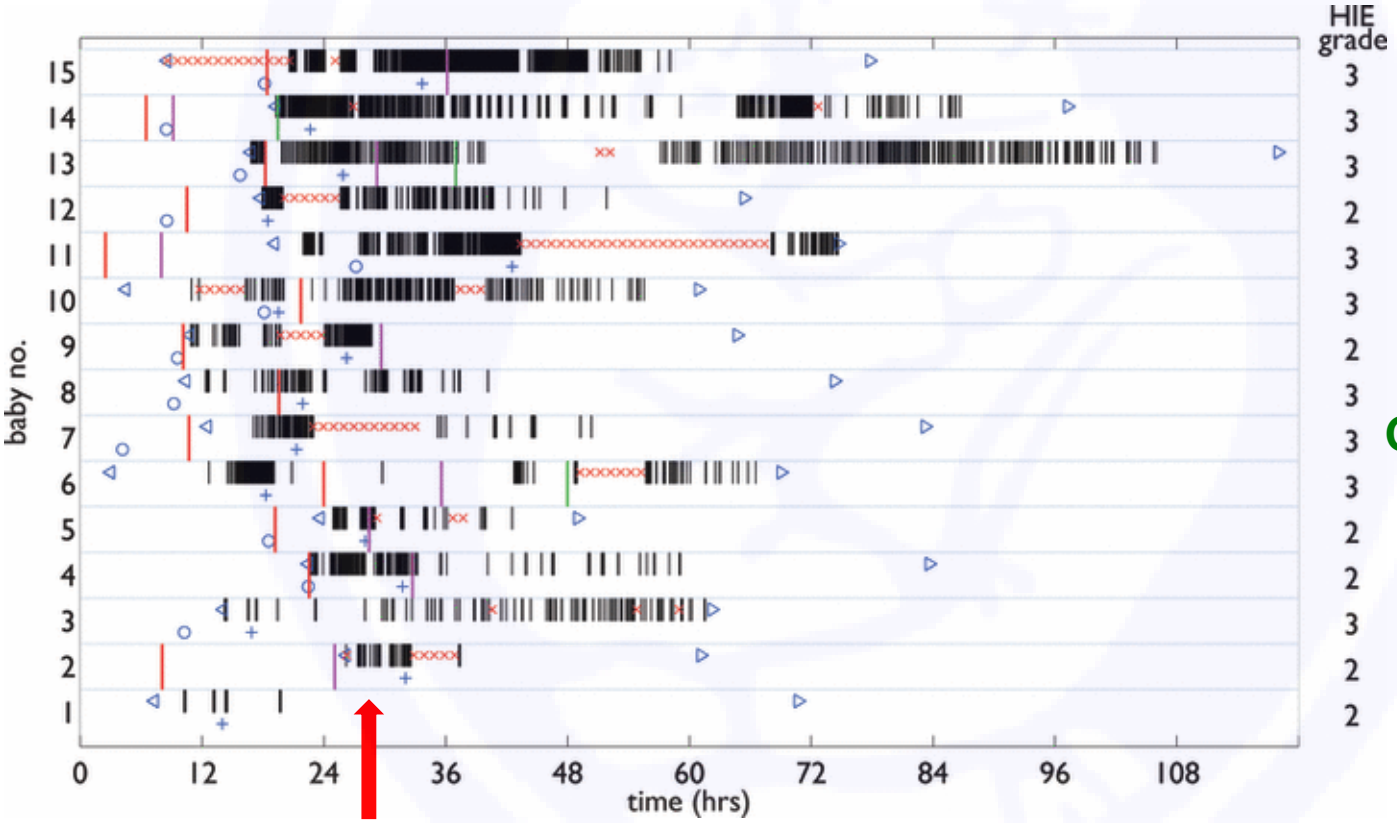
1. PB/PHT most effective for newborns with fewest seizures
   - 88% with mild seizures
   - 10% with severe seizures
2. PB/PHT most effective if seizures subsiding
   - 81% with decreasing seizure frequency
   - 30% with increasing seizure frequency

➢ Apparent drug effect may be instead seizures naturally subsiding

- (Trials should test drugs early in newborns with high seizure burden)

Timing of EEG seizures in neonatal HIE

Lynch Epilepsia 2012



Vertical lines =
Black = seizures
Loading doses:
Red = PB
Magenta = PHT
Green = Midazolam

High seizure burden early, usually resolve within 48-96 hours

Epilepsia Volume 53, Issue 3, pages 549-557, 6 FEB 2012 DOI: 10.1111/j.1528-1167.2011.03401.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2011.03401.x/full#f1

Levetiracetam (LEV)

Retrospective study of levetiracetam

- Khan Ped Neuro 2011

- Limitations:
  - 55% no EEG confirmation of seizures
  - 86% pretreated with ≥1 AED
  - No EEG monitoring of response to LEV
- Reported that 64% of 22 newborns had no clinical seizures by 24 hours, 86% by 48h

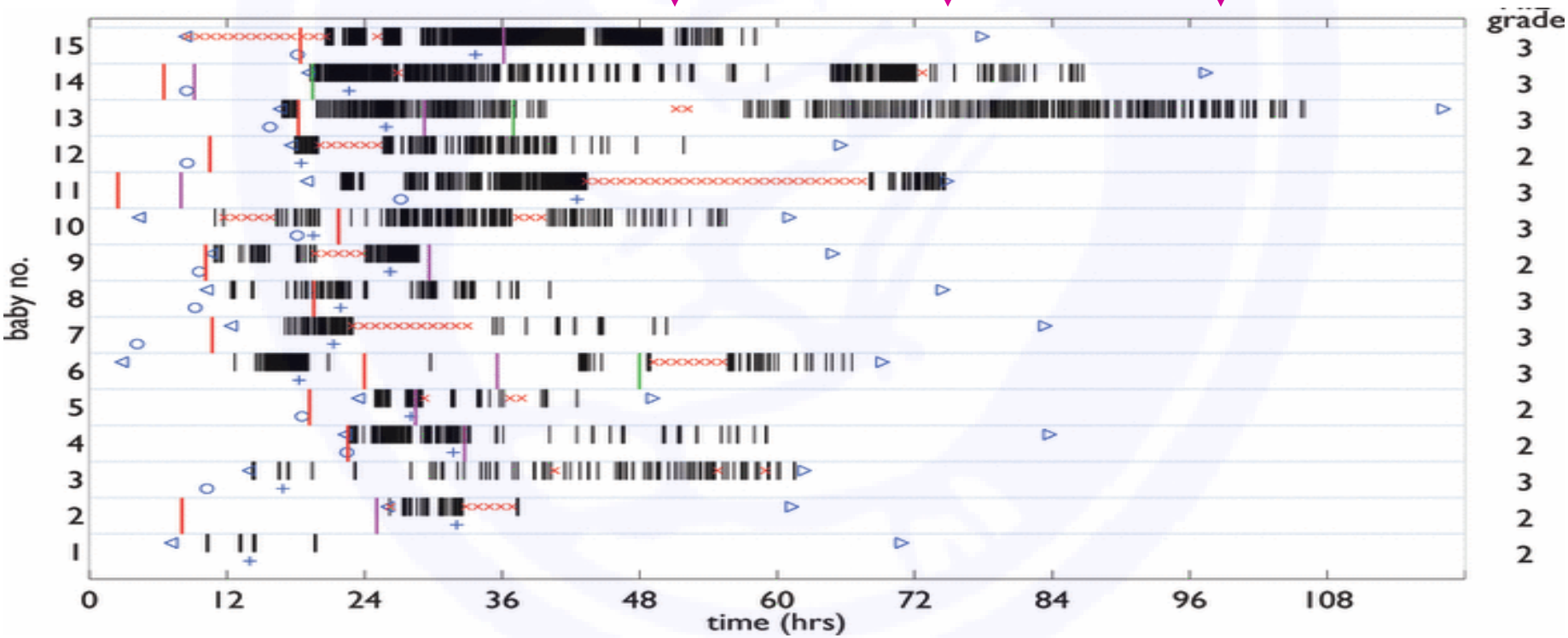
Study of Levetiracetam

Khan et al. Ped Neurol 2011

Seizure cessation after levetiracetam

32% 1 hr **64% 24 hr** **86% 48 hr**

86% pre-tx'd for mean of 36h



Lynch *Epilepsia* 2012

Levetiracetam Trial

NCT01720667 Sharpe Pediatrics 2020

- Trial compared LEV 40-60 mg/kg to Phenobarbital 20-40 mg/kg as first line
  - Randomized, double- masked
  - Continuous video-EEG monitoring
- If seizures continued, subjects crossed over to receive other drug

➢ Phenobarbital much more effective than levetiracetam

Sharpe *Pediatrics* 2020

Levetiracetam Trial

NCT01720667: Sharpe *Pediatrics* 2020

Seizure cessation (% of newborns)

Time (hours)	Phenobarbital	Levetiracetam
1 h	93	49
24 h	80	28
48 h	64	17
Efficacy as 2nd line drug	54	17

Levetiracetam Trial

NCT01720667: Sharpe *Pediatrics* 2020

- Reported more adverse events with PB vs LEV
  - Only statistically significant difference was hypotension in 7(17%) PB vs. 3(5%) LEV
  - No significant difference in serious adverse events
- High treatment success in PB group:
  - Likely faster treatment than Painter trial
  - Maybe lower seizure severity?

➢ Phenobarbital superior to Levetiracetam as first or second line drug

Lidocaine: Retrospective Study

Weeke Epilepsia 2015

- 22-year study of 319 term, 94 preterm:
  - 21% had 'good response: no or short seizures, no need for rescue drug
  - 51% with 'intermediate response': recurrence of seizures within 2-4h or treated with rescue drug
  - Less effective in preterm than term

2nd vs. 3rd line drugs

- Lidocaine as 2nd or 3rd drug
- 3rd drug "works better": seizures subsiding
- Longer lag time correlated with 'good' effect

Subjects	Lido 2nd (N=131)	Lido 3rd (N=145)
Term newborns (n= 296)	28 (21%)	98 (68%)
HIE only (n~190)	17 (20%)	50 (66%)

Weeke Epilepsia 2015

Midazolam

- Efficacy data: few and weak
- Retrospective study of midazolam IV infusion, n= only 13!
  - Reported seizure cessation in 100%
  - Newborns received PB & PHT first
    - CastroConde Neurol 2005
- From retrospective study of lidocaine
  - Midazolam had 'good' response rate in only 13% as second-line drug
    - Weeke Epilepsia 2015

2nd vs. 3rd line drugs

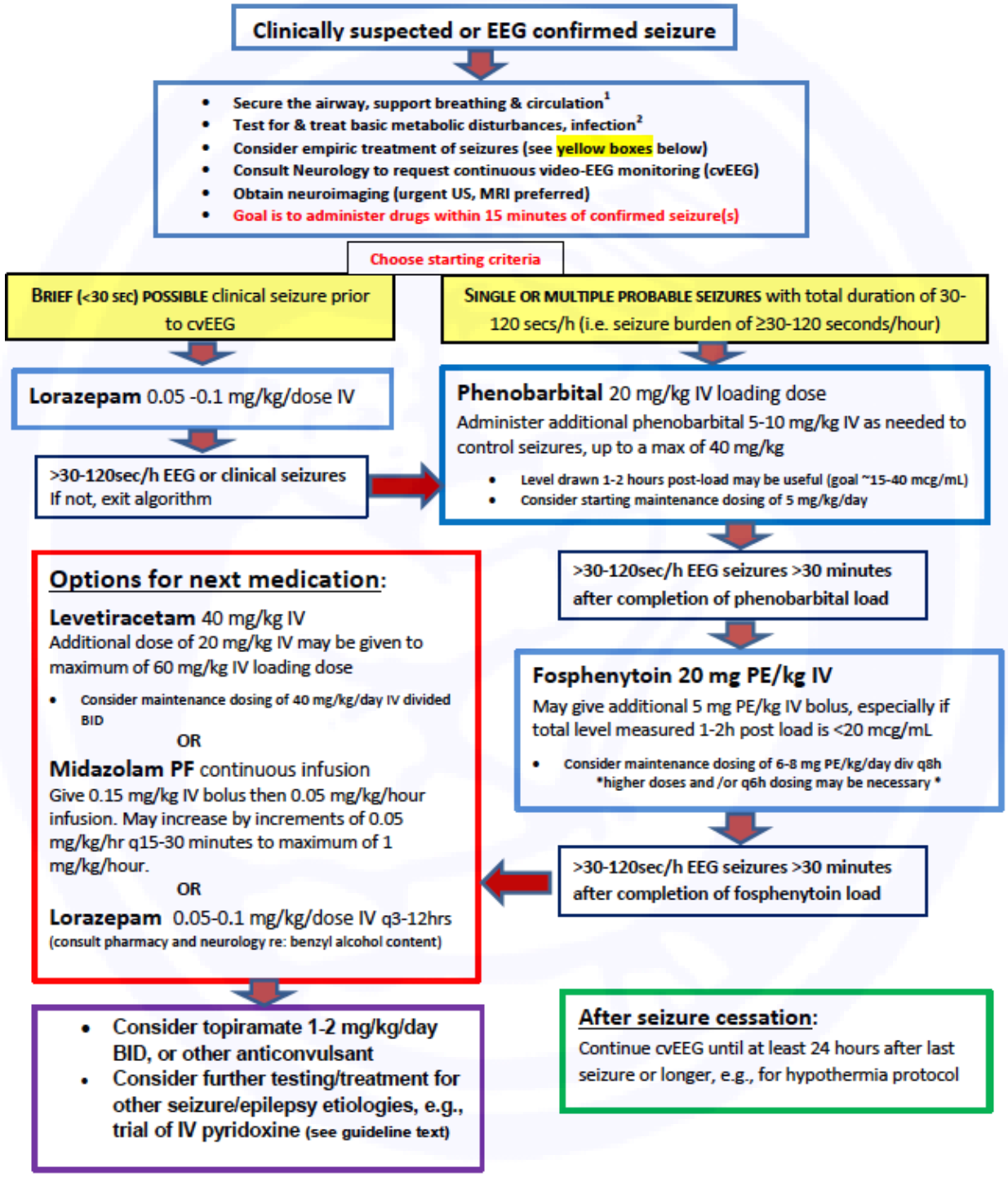
- Midazolam as 2nd or 3rd drug

Subjects	MDZ 2nd (N=131)	MDZ 3rd (N=107)
Term newborns (n= 296)	21 (13%)	61 (57%)
HIE only (n~190)	12 (14%)	42 (58%)

Weeke Epilepsia 2015

BCH Neonatal Seizure Protocol

- **BCH Neonatal Seizure Protocol**
  - **Algorithm for quick reference**
  - **Text describes rationale, further details regarding management of symptomatic seizures or neonatal onset epilepsy**



Acute seizure management

- Emergency!!!
  - Airway, breathing & circulation
- Test for and treat basic metabolic disturbances, infection
  - Labs: ABG, electrolytes, CBC
    - Correct glucose, electrolyte abnormalities
  - Blood and CSF cultures ± HSV PCR and viral cultures
  - Administer antibiotics ± acyclovir

Acute seizure management: EEG

1. cvEEG needed to diagnose seizures
   a) ~50% of clinical spells aren't seizures
   b) Subclinical seizures very frequent!

2. cvEEG needed to assess drug response
   Drugs may suppress clinical seizures, but EEG seizures persist

3. Goal to administer drugs within 15 minutes of confirmed seizure(s)

Acute seizure management: cvEEG

ACNS guideline:

– Shellhaas J Clin Neurophys 2011

- Minimum 24 hours cvEEG for newborns with suspected seizures or high risk of seizures (e.g., HIE)

- Continue cvEEG at least 24 hours after last seizure

Acute seizure management

1. Consider lorazepam for brief clinical/ suspected seizures, <30s, before cvEEG
2. Phenobarbital 20 mg/kg IV
3. If continued seizures, additional 5-10 mg/kg doses of phenobarbital
   - Total load up to ~40mg/kg or level ~40
   - PB levels >>40 result in sedation, depressed respiration, with prolonged clearance
4. Phenytoin 20 mg/kg IV (+5-10mg/kg)
   - Maintenance dosing often needs to be >6mg/kg/d ÷ TID-QID to maintain good level

Acute seizure management

After PB & PHT loads, there are several options with limited supportive data:

- Levetiracetam
  - Consider 40-60mg/kg loading dose
  - Data from trial showed low efficacy
- Midazolam infusion
  - Consider if status epilepticus
- Lorazepam 0.05-0.1 mg/kg q3-12 hours
- Consider lidocaine infusion if you have experience using it
- Topiramate if enteral drugs possible

Brain imaging

- Prioritize seizure treatment before imaging!
- Brain MRI: best imaging modality for term & preterm newborns with seizures
  - Delineates parenchymal abnormalities
- US first for preterm, or critically ill term
  - US to rule out large ICH if MRI can't be obtained quickly, or if frequent seizures
- Avoid CT unless neurosurgical emergency suspected and can't obtain fast US or MRI

Intractable Seizures +/- Encephalopathy and Unknown Etiology

- Consider metabolic disorder
  - Send CSF for glucose, protein, lactate, pyruvate, amino acids and neurotransmitters
  - Obtain serum glucose, lactate/pyruvate & amino acids at the same time as CSF
  - Consider serum homocysteine, uric acid, VLCFA, pipecolic acid, carnitine and acyl carnitines, carbohydrate deficient transferrin & CDG panel
- Consider genetic epilepsy syndrome
  - Epilepsy gene panel test (stat panels ideal)
- Consider subtle brain malformation
  - may need high resolution MRI at older age

Empiric Treatment of Seizures of Unknown Etiology

- Send CSF neurotransmitter tests first
- Pyridoxine (B6) 100mg IV x1-2 dose
  - During cvEEG with respiratory monitoring as apnea can occur with B6 dependent epilepsy
  - continue maintenance dose of 15-30 mg/kg/d
- If no response, consider empiric trials of:
  - Pyridoxal-5-Phosphate (P5P), 30-60 mg/kg/d divided q4-6h
  - Folinic acid 3-5 mg/kg/d divided q6-8h
  - Biotin 5-10 mg qday

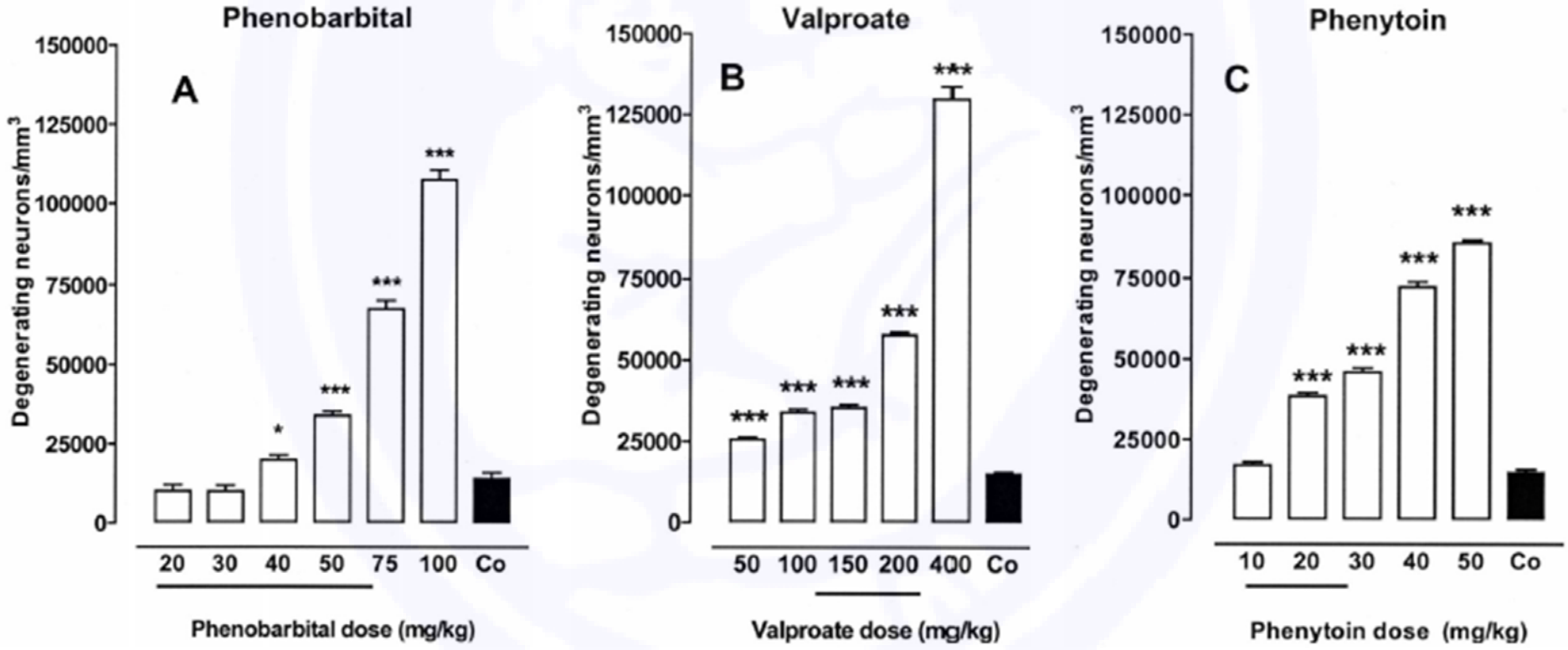
Empiric Treatment of Seizures of Unknown Etiology

- **Possible genetic epilepsy**
  - **If newborn relatively well, no encephalopathy, normal EEG background +/- family history**
    - **Possible KCNQ2/3 gene variant**
    - **Try sodium channel blockers, e.g., phenytoin, oxcarbazepine, carbamazepine**
  - **If severely encephalopathic or with frequent seizures, could be SCN1A, SCN2A, CDKL5, MANY other genes, or metabolic disorder**
    - **AVOID sodium channel blockers for SCN1A**

Duration of drug treatment: Acute symptomatic seizures

- Clinical trial failed to enroll (PROPHENO)
- Rationale to discontinue drugs early:
  - Minority (~20-40%?) develop later epilepsy
  - Use different drugs to treat seizures at older age
  - Possible harm of prolonged drug administration on cognition, development
- Comparative Efficacy study by NSR group
  - Non-inferior developmental outcome
  - Post-neonatal seizures unaffected by Rx
    - Median age of onset 8 months
      - » (Submitted for publication)

Animal data show harm of drugs for neonatal seizures:
Apoptosis in P7 rats



Bittigau Ann NY Acad Sci 2003

Duration of drug treatment: Neonatal-onset epilepsy

- Treatment of underlying metabolic disorder +/- antiseizure drugs as needed
- Continue targeted antiseizure drug(s) if specific genetic epilepsy gene known
- Continue antiseizure drugs to control seizures for brain malformations, other presumed/known genetic etiologies

Prognosis

- Neonatal onset epilepsy
  - Benign familial neonatal epilepsy
    - Many neonates have no further seizures
    - Some develop generalized seizures later
  - Neonatal epileptic encephalopathy
    - Depends on gene variant
    - Early death or severe developmental disability
    - Intractable epilepsy frequent
- Acute symptomatic seizures:
  - Up to 40% (or more?) have later epilepsy
  - Disability predicted by etiology, brain injury detected by MRI & seizure severity

Summary

- **Neonatal Seizures:**
  - **Increase risk for later epilepsy**
  - **Probably exacerbate brain injury, disability**
- **Limited high quality data from randomized trials regarding efficacy or safety of drugs**
- **Evidence suggests that prompt, effective treatment improves outcome**
- **Need more well designed, randomized trials with a control group to test new drugs!**

State of the Art Guidelines

- ACNS guideline for neonatal EEG
  - Shellhass R, Journal Clinical Neurophysiology 2011
- Recommendations for Neonatal Seizure Trial Design by the International Neonatal Consortium
  - Soul JS Pediatric Research June 2019 (online now)
- AAP guideline for therapeutic hypothermia for neonatal encephalopathy
  - Pediatrics 2014

Additional Resources

- **Seminars In Fetal and Neonatal Medicine**
  - **Entire Issue on Neonatal Seizures**
  - **June 2018**
- **Including:**
  - **Acute Symptomatic Seizures**
  - **Neonatal onset /genetic epilepsy**
  - **EEG monitoring, diagnosis**
  - **Outcome of Neonatal seizures, etc**

What's new in neonatal seizures and neonatal-onset epilepsy

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Director, Fetal - Neonatal Neurology Program
Boston Children's Hospital
Associate Professor of Neurology
Harvard Medical School