

Neonatal Seizures

The Tip of the Iceberg

Courtney Wusthoff, MD MS

Assistant Professor, Neurology

Neurology Director, LPCH Neuro NICU



Stanford
Children's Health

Lucile Packard
Children's Hospital
Stanford



Stanford | MEDICINE

Disclosures

- I have no conflicts of interest
- I will discuss off-label use of anti-epileptic drugs (AEDs) for treatment of neonatal seizures

Acknowledgements

Nick Abend

Bob Clancy

Don Olson

Learning Objectives

At the conclusion of this activity, participants should be able to...

1. Recognize the challenges in diagnosing neonatal seizures.
2. Identify risk factors for neonatal seizures.
3. Compare the risks and benefits of common treatments for neonatal seizures.

Overview

- Do Seizures Matter?
- Diagnosis of Neonatal Seizures
- Management of Neonatal Seizures

Overview

- Do Seizures Matter?
- Diagnosis of Neonatal Seizures
- Management of Neonatal Seizures

Baby Transferred for Cooling...

- Term born girl born via crash caesarean section after cord prolapse
- Apgars 1, 2, 4, 6
- Transferred to your hospital for therapeutic hypothermia
- Day 1: the resident notices some “jittery” movements that she notes might be shivering, or perhaps clonus?
- Does it really matter if these are seizures?



Stanford
Children's Health

Lucile Packard
Children's Hospital
Stanford



Stanford | MEDICINE

How could we find out if neonatal seizures are harmful or not?

- Animal Studies
- Examine the way seizures affect brain metabolism and MRI findings
- Follow babies with seizures and compare outcomes to sick babies without seizures

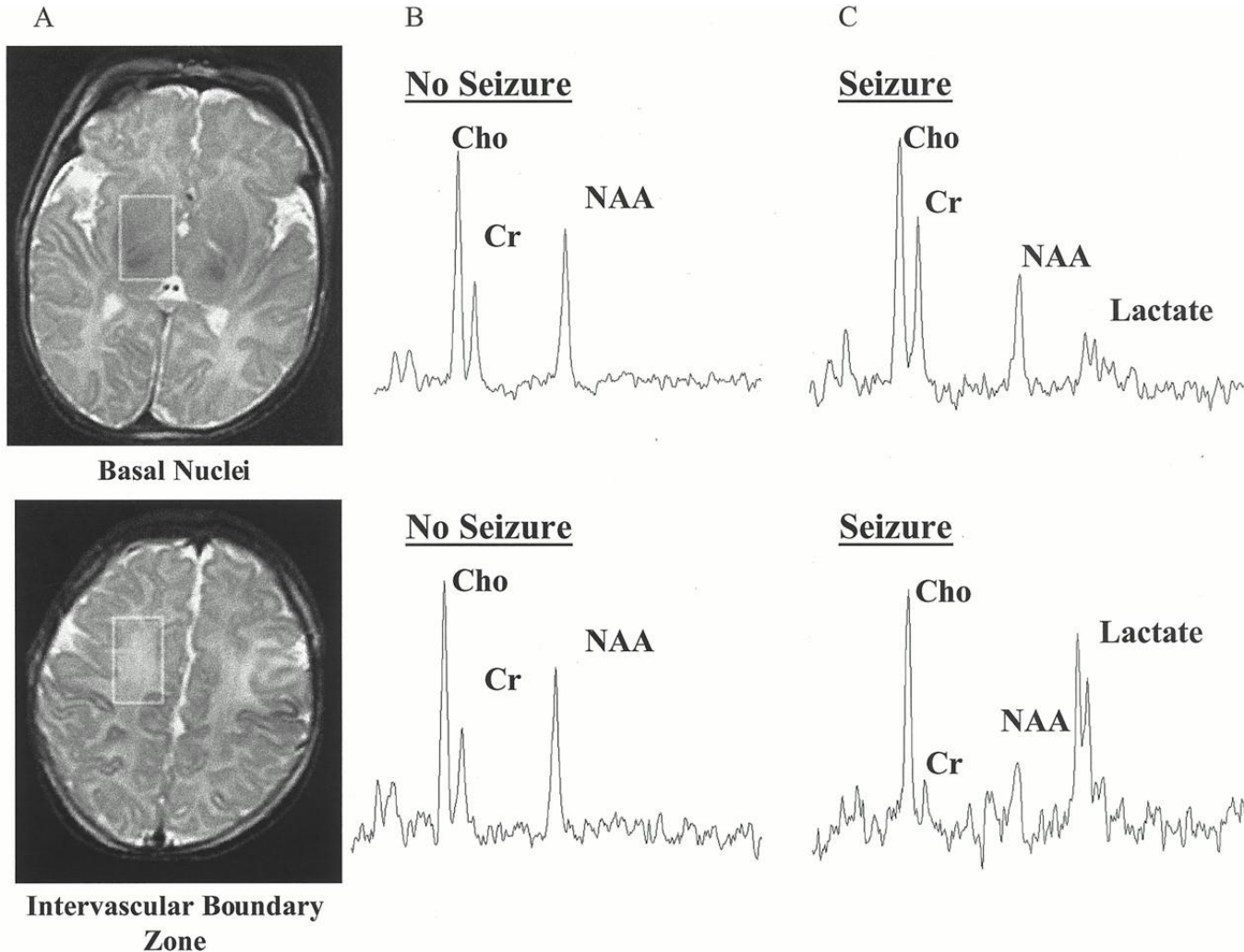
Subclinical seizures: effects on intracranial pressure (ICP) & brain lactate levels

Table 3. Intracranial pressure (ICP) before and after seizure

Patient	Interictal ICP	Ictal ICP	Delta ICP with Seizure	Interictal LPR	Ictal LPR	Ictal % LPR >40
1	12	25	13	38	50	18
2	17	35	18	20	35	62
3	6	25	19	20	60	23
4	14	22	8	18	33	1
5	8	25	17	18	25	9
6	16	25	10	18	41	36
7	6	18	12	16	70	33
8	2	10	8	29	70	94
9	5	14	8	29	60	36
10	10	25	15	32	50	38
Ave \pm SD	9.6 \pm 5	22.4 \pm 7	12.8 \pm 4.3	23.8 \pm 7.6	49.4 \pm 16	35 \pm 27

In adults with traumatic brain injury, ICP and lactate/pyruvate ratio significantly higher during than between seizures.

Biomarkers of injury in neonatal seizures



- 90 babies with HIE

- 33 with seizures

- MRI d 1-13

- Dose effect with worse seizure score associated with higher lactate/choline

Miller SP et al. Neurology 2002;58:542-548

Neonatal Seizures and Outcomes

Untreated seizures are suspected to contribute to worsened outcomes.

- Among at-risk neonates, presence of seizures, greater number of seizures, and longer duration all correlate with worse outcomes
 - For every 1-min increase of total seizure burden, odds of abnormal outcome increase by 2.2%*
 - For every 1-min increase in maximum hourly seizure burden, the odds of an abnormal outcome increase by 16%.*
- Among neonates with seizures, those with status epilepticus are more likely to have later epilepsy and neurodevelopmental disability

Neonatal Seizures and IQ at 4 years

- 77 term neonates with Hypoxic Ischemic Encephalopathy.
- Analysis stratified by:
 - Seizure severity:
 - Scored 0-10 by a single reader based on seizure number, duration, time of onset, AED responsiveness, EEG background and EEG seizures.
 - Severity of HIE as seen on MRI:
 - All babies scanned in the acute period; scored using a validated method
- Full Scale IQ (FSIQ) at 4 years lower with seizures, evidence for a dose effect, even after correction for MRI

FSIQ score, mean (95% CI)	Severe seizures (n = 11)	Mild/moderate seizures (n = 14)	No seizures (n = 52)	P*
Unadjusted	64.7 (52.6 to 76.9)	83.1 (72.4 to 93.9)	100.2 (94.6 to 105.8)	< .0001
Adjusted†	67.2 (54.6 to 79.8)	82.7 (72.7 to 92.7)	96.9 (90.7 to 103.1)	.001

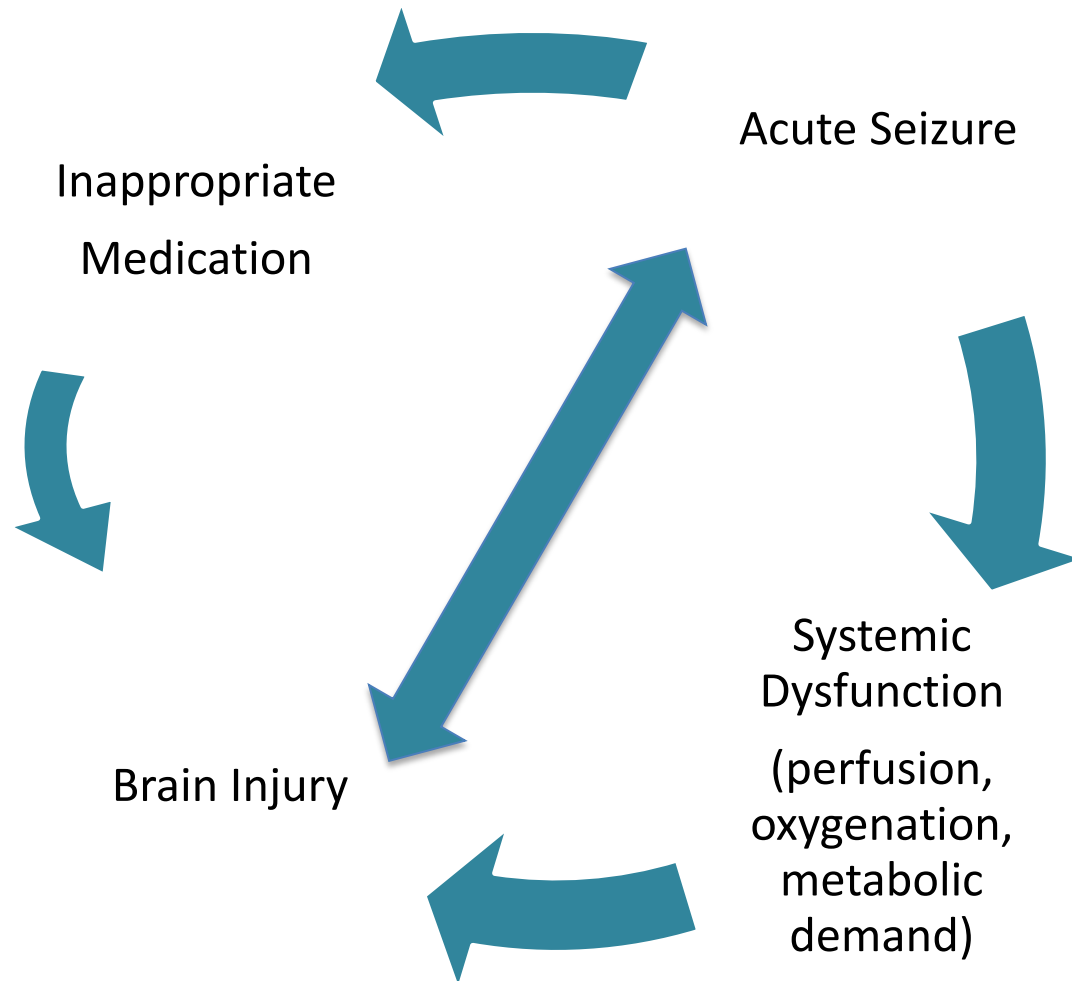
Seizures Associated with Outcome in CHD

- The Boston Circulatory Arrest Study
- Continuous EEG (cEEG) recorded for 48 hours after repair of Transposition of the Great Arteries (TGA)
- EEG seizures (19%) 3x more common than clinical seizures (6%).
 - Most infants with EEG seizures had multiple seizures, beginning between 13 and 36 h postoperatively.
- EEG seizures were not read as clinical studies, but were read later as research studies
- EEG seizures appeared in 25 of 126 (20%) infants
 - were associated with an 11.2 point drop on Bayley PDI scores @ 1 year ($p=0.002$)

Seizures still affecting outcomes at later follow up

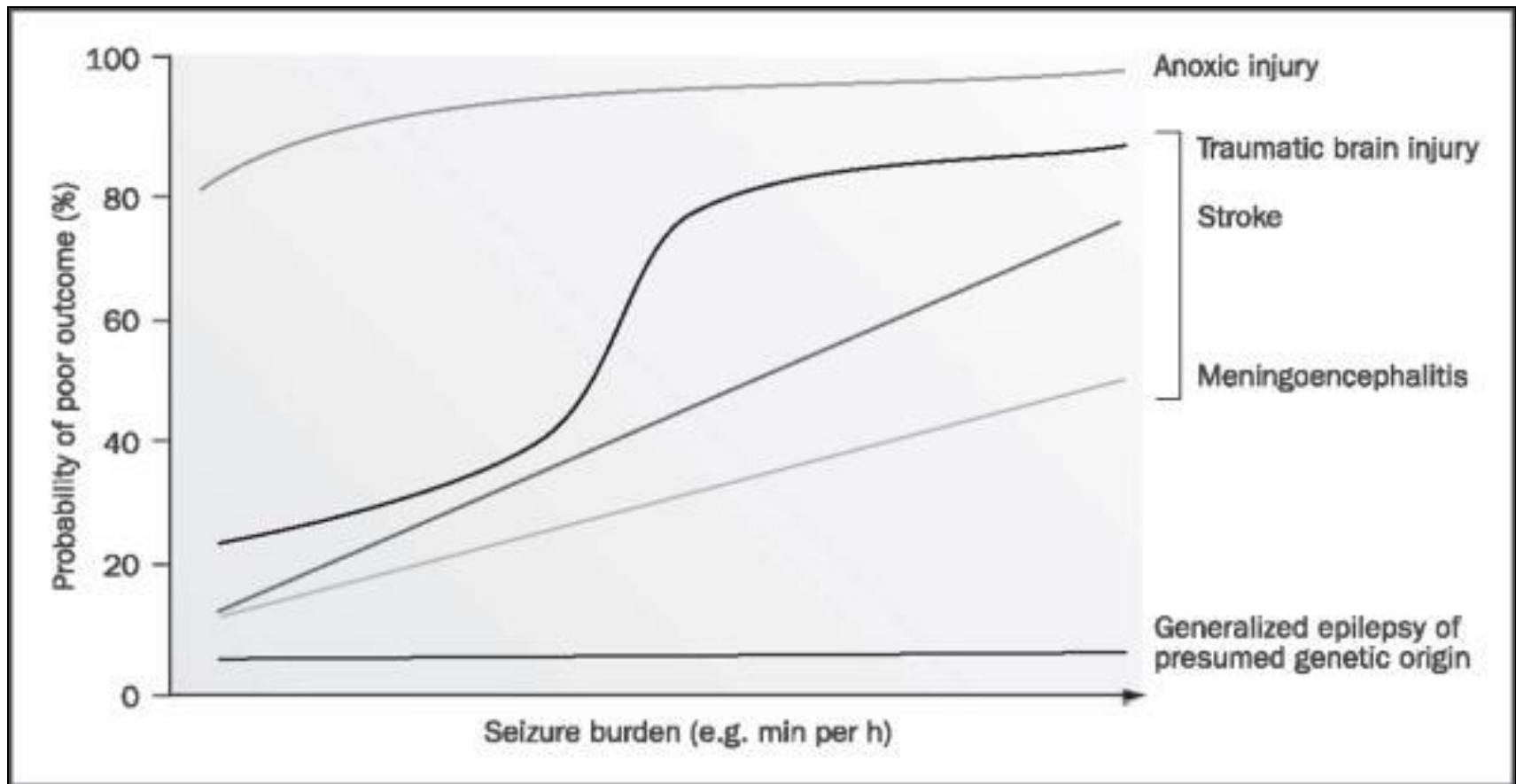
- At 4-year follow up:
 - Seizures in the perioperative period, detected either clinically or by cEEG, were associated with lower mean IQ scores (12.6 and 7.7 points, respectively)
 - Seizures associated with increased risk of neurological abnormalities (odds ratios, 8.4 and 5.6, respectively).
- At 16-year follow up
 - “The occurrence of seizures in the postoperative period was the medical variable most consistently related to worse outcomes.”

Impact of non-convulsive seizures



Influence of etiology

Schematic



Outcomes following electrographic seizures and electrographic status epilepticus in the pediatric and neonatal ICUs. Pinchevsky, Elana; Hahn, Cecil. *Current Opinion in Neurology*. 30(2):156-164, April 2017.

Baby Transferred for Cooling...

- Term born girl born via crash caesarean section after cord prolapse
- Apgars 1, 2, 4, 6
- Transferred to your hospital for therapeutic hypothermia
- Day 1: the resident notices some “jittery” movements that she notes might be shivering, or perhaps clonus?
- Does it really matter if these are seizures?

Overview

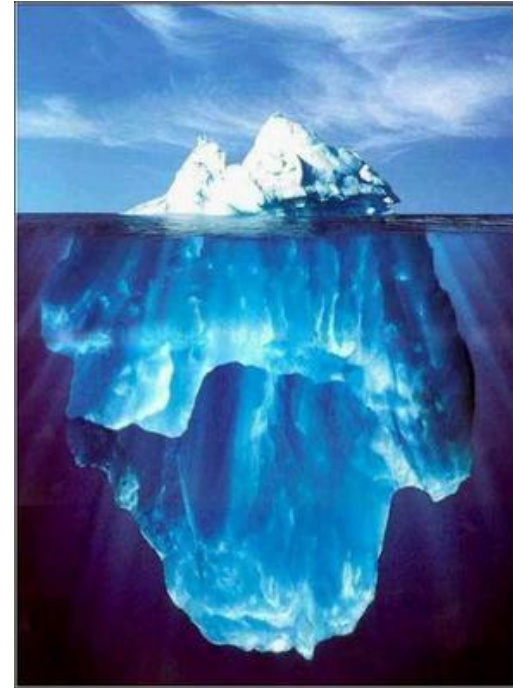
- Do Seizures Matter?
- Diagnosis of Neonatal Seizures
- Management of Neonatal Seizures

Problems after Surgery...

- Your patient is a 36-week boy with congenital heart disease now recovering after surgery on day 3
- He is sedated and paralyzed on a ventilator
- Throughout the day, there are paroxysmal spikes in heart rate and blood pressure without explanation.
- Are these seizures?

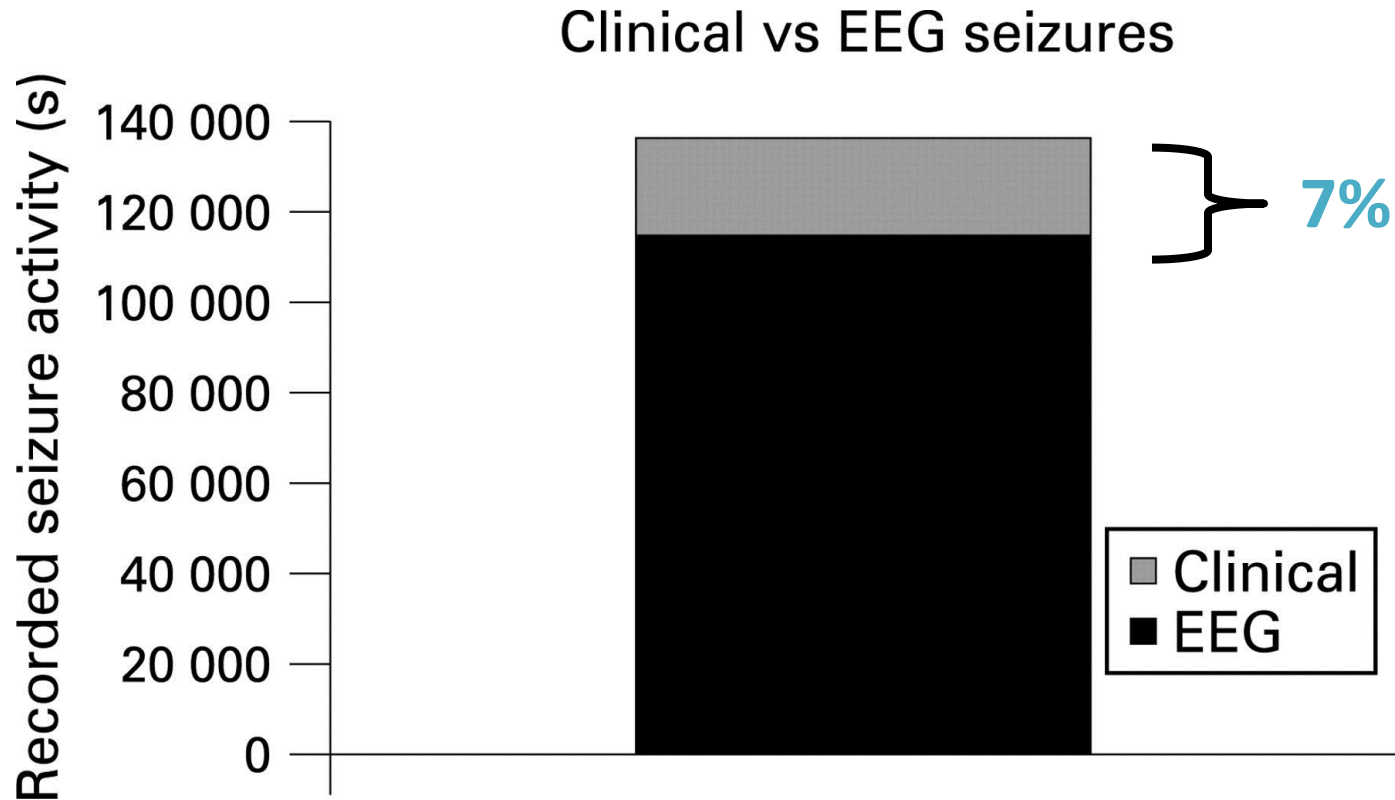
Suspected Seizures

- 1-5 per 1000 in term newborns
- Unclear for NICU preterms
 - Clinically: 1 in 200 ¹
 - On aEEG: Up to 48%²⁻⁴
 - On continuous video EEG: 5%⁵
- Diagnosis is a challenge
 - Up to 85% of neonatal seizures have **no** clinical signs
 - 1/3 of neonates with seizures have **only** subclinical seizures
 - Up to 74% of suspected clinical seizures are **not** epileptic seizures.
- Electroclinical “uncoupling” is common
 - 42-58% after phenytoin or phenobarbital
- Overtreatment is not benign.
 - Overuse of seizure meds prolongs length of stay
 - Prophylactic seizure medications associated with increased morbidity



1. Davis AS. J Pediatr 2010
 2. Shah DK Pediatr Res 2010
 3. Wikstrom S Acta Pediatr 2012
 4. Vesoulis ZA Pediatr Res 2013
 5. Lloyd RO. J Pediatr 2017
- Clancy, Legido & Lewis Epilepsia 1988
Mizrahi & Clancy, Epilepsia 2001
Miller, Neurology 2002
McBride, Neurology 2000
Pisani, Neurology 2007
Wyatt, Pediatrics 2007
Glass, J Pediatr 2009

Total Recorded Electrographic Seizure Activity Versus Total Duration of Observed Clinical Seizures in Nine Patients Recorded by Continuous Video-EEG During the First 72 Hours of Life



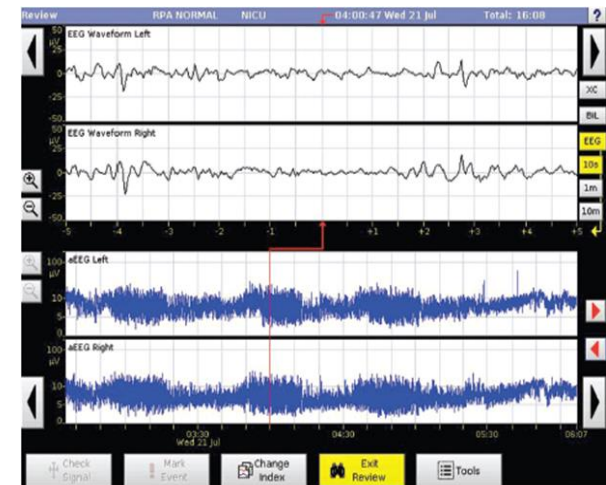
Murray, D M et al. Arch. Dis. Child. Fetal Neonatal Ed. 2008;93:F187-F191

Continuous EEG (cEEG) is the Gold Standard for Diagnosis

- Traditional 60 minute EEG is limited for capturing seizures
 - Many high risk neonates have no seizures in the first hour of monitoring, but will have seizures if recording is continued for 24 hours
 - In HIE, up to 50% of seizures start after the first 24 hours
 - In cooling, ~5% will have seizures only during rewarming
- Seizure medicines cause “uncoupling”- the outward signs go away, but the seizure continues
 - Uncoupling observed in 50-60%
- Also a high risk of overdiagnosis based on clinical signs alone
 - Jitteriness, sleep myoclonus, abnormal movements, vital sign fluctuations
 - One series found 73% of “clinical seizures” documented in nursing notes had no EEG correlate

aEEG for Seizure Detection

- Dual channel aEEG with raw EEG can identify 40-90% of patients with seizures
- aEEG identifies 12-80% of individual seizures
 - Highly dependent on user experience
 - Dependent on availability of raw EEG for confirmation
 - Shorter seizures more likely missed
- aEEG alone may overpredict seizures 50-100%
- Artifact can interfere with interpretation
 - Significant artifact present in 12-60% of records
 - Especially if artifact outside 2-15 Hz range
- Typically, raw EEG is available, but must set options to display it



Single-Channel aEEG for Neonatal Seizure Detection

Table 1. Single-Channel Amplitude-Integrated Electroencephalography (EEG) for Neonatal Seizure Detection.

Author	Patients with seizures, n	Controls without seizures, n	Individual seizures, n	Amplitude-integrated EEG reader experience	Sensitivity for individual seizures	Sensitivity for seizure-positive records	Specificity
Rennie et al ³¹	19	21	Not reported	Novice	38%	4/19 correctly identified by all 4 observers	92%
Shellhaas et al ²⁶	125	19	851	Varied	25.5% \pm 10.6%	40.3% \pm 16.8%	Not reported
Shah et al ^{28,a}	7	14	41	Expert	27%-56%	85%	Not reported
Frenkel et al ³⁰	10	28	41	Varied	71%-84% ^b	68%-84%	0.39-0.96

a. Adding a second amplitude-integrated EEG channel, with corresponding raw EEG data, improved the sensitivity in this study (but without the raw EEG data, sensitivity remained poor).

b. Used single-channel EEG with access to raw single-channel EEG data.



Glass H C et al. J Child Neurol 2013;0883073813488663

www.acns.org/guidelines.cfm

ACNS GUIDELINE

The American Clinical Neurophysiology Society's Guideline on
Continuous Electroencephalography Monitoring in Neonates

Renée A. Shellhaas, Taeun Chang,† Tammy Tsuchida,† Mark S. Scher,‡ James J. Riviello,§ Nicholas S. Abend,||
Sylvie Nguyen,¶ Courtney J. Wusthoff,# and Robert R. Clancy||*

J Clin Neurophysiol 2011;28: 611-617

High-Risk Conditions for Seizures

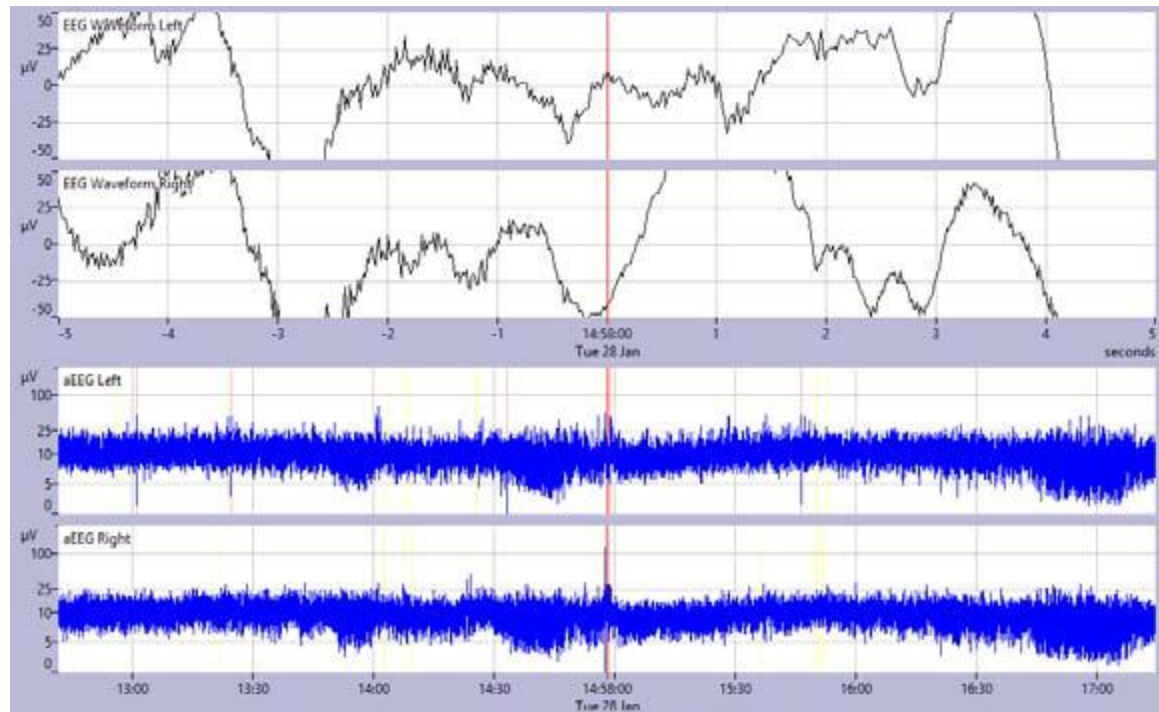
CATEGORY	EXAMPLES
Acute neonatal encephalopathy	HIE, postnatal collapse
Cardiac or pulmonary risk for brain injury	ECMO, congenital heart defects perioperatively
CNS infection	Meningitis, encephalitis
CNS trauma	Subarachnoid bleeding, nonaccidental trauma
Inborn errors of metabolism	Various
Stroke	Arterial stroke, venous thrombosis
At-risk preterm infants	Acute IVH
Genetic/syndromic disease	Cerebral dysgenesis, multiple anomalies with encephalopathy

Problems after Surgery...

- Your patient is a 36-week boy with congenital heart disease now recovering after surgery on day 3
- He is sedated and paralyzed on a ventilator
- Throughout the day, there are paroxysmal spikes in heart rate and blood pressure without explanation.



Problems after Surgery...



Overview

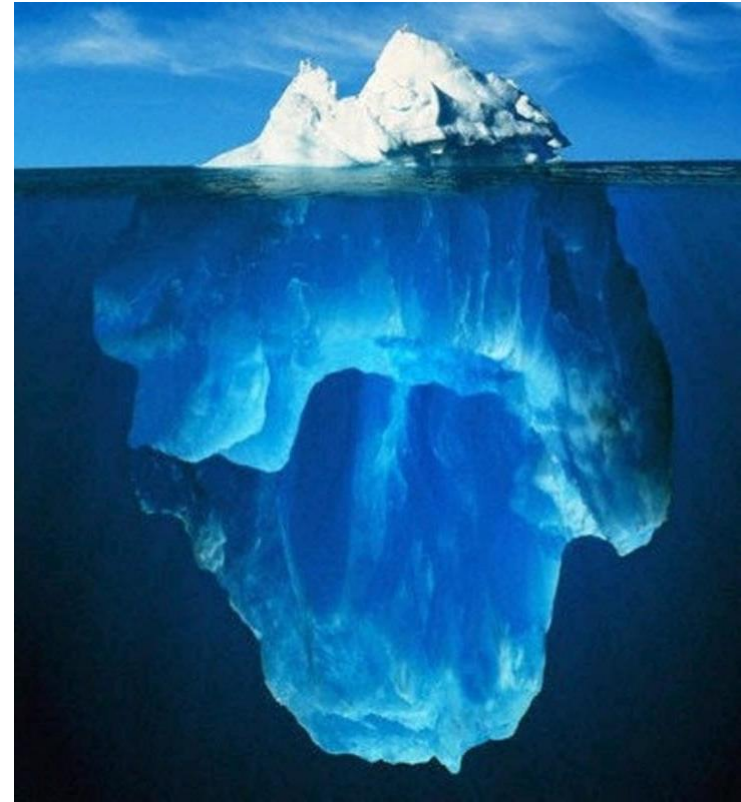
- Do Seizures Matter?
- Diagnosis of Neonatal Seizures
- Management of Neonatal Seizures

A Patient is Admitted from the ER...

- Term born boy to a G1P1 28-year old mother
- Uncomplicated pregnancy; good prenatal care
- Delivery was vacuum-assisted vaginal following decelerations in the second stage
- Apgars 3, 5, 9
- Discharged home with mom day 2
- Day 4: three episodes of dusiness and funny breathing prompting parents to come to ED

Most Neonatal Seizures are Symptomatic

- ~80% of neonatal seizures are symptomatic of acute brain injury
- Common causes:
 - Cerebral hypoxia-ischemia (~50% in US)
 - Stroke/hemorrhage (15-30%)
 - Infection
 - Malformations
 - Electrolytes/hypoglycemia
- ~20% due to early-onset epilepsy
 - KCNQ2 mutations most common
 - Brain malformations/other syndromes



Evaluation for Cause of Seizures

- Acutely: head ultrasound, basic labs, EEG
- As soon as possible: MRI
 - ~90% will have diagnosis by MRI
 - acute brain injury or structural abnormality
- If MRI normal:
 - Is there a benign or malignant EEG pattern?
 - Any clinical signs to indicate a particular diagnosis?
 - Genetic testing identifies a cause in >60% when MRI is normal

A Patient is Admitted from the ER...

- Term born boy to a G1P1 28-year old mother
- Uncomplicated pregnancy; good prenatal care
- Delivery was vacuum-assisted vaginal following decelerations in the second stage
- Apgars 3, 5, 9
- Discharged home with mom day 2
- Day 4: three episodes of dusiness and funny breathing prompting parents to come to Emergency Department
- **Found to have a KCNQ2 mutation**

Principles of Management

- Confirm “seizures” are seizures.
- Look for a cause as you treat
- Treat early and consistently.
 - Status Epilepticus is a neurological emergency
 - Untreated seizures may contribute to worsened outcomes.
 - Overtreatment is not benign.
- Be explicit about goals of treatment.

Goal of Treatment

- Complete resolution of seizures on EEG?
- Reduction of seizure burden?
- Reduction of clinical seizure burden?



Conventional Approach

Phenobarbital

- 20 mg/kg load x1-2 (to level of 40*)
- 4-6 mg/kg/d maintenance

Phenytoin

- 15-20 mg/kg load x1 (to level 15-20*)
- 5-10 mg/kg/d maintenance

Benzodiazepine

- Lorazepam: 0.1mg/kg
- Midazolam infusion

~15-20 minutes between steps

*Post-load levels 1-2 hours after

Trends in Treatment Selection

	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	P-value for trend
	n=2044	n=2008	n=1688	n=1781	n=1613	
Phenobarbital (%)	2031 (99.4%)	1980 (98.6%)	1656 (98.1%)	1743 (97.9%)	1554 (96.3%)	<0.001
Phenytoin (%)	301 (14.7%)	312 (15.5%)	233 (13.8%)	207 (11.6%)	178 (11.0%)	<0.001
Levetiracetam (%)	28 (1.4%)	119 (6.0%)	171 (10.1%)	190 (10.7%)	230 (14.3%)	<0.001
Carbamazepine (%)	11 (0.5%)	11 (0.6%)	5 (0.3%)	0 (0%)	3 (0.2%)	0.0025
Lidocaine (%)	9 (0.4%)	10 (0.5%)	9 (0.5%)	4 (0.2%)	7 (0.4%)	0.544
Topiramate (%)	0 (0%)	2 (0.1%)	4 (0.2%)	5 (0.3%)	0 (0%)	0.3579

Pediatrix Data. From Changing antiepileptic drug use for seizures in US neonatal intensive care units from 2005 to 2014. J Perinatology. K A Ahmad, S J Desai, M M Bennett, S F Ahmad, Y-T Ng, R H Clark and V N Tolia

Trends in Treatment Selection

	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	P-value for trend
	n=229	n=271	n=253	n=270	n=282	
Medication order						
Phenobarbital–phenytoin	184 (80%)	168 (62%)	118 (47%)	114 (42%)	101 (36%)	<0.0001
Phenobarbital–levetiracetam	13 (6%)	52 (19%)	85 (34%)	113 (42%)	137 (49%)	<0.0001
PB–PHT–LVT	7 (3%)	16 (6%)	18 (7%)	12 (4%)	9 (3%)	0.7016
PB–LVT–PHT	1 (0.5%)	10 (4%)	10 (4%)	14 (5%)	8 (3%)	0.096
Levetiracetam–phenobarbital	2 (1%)	1 (0.4%)	5 (2%)	8 (3%)	12 (4%)	0.0007
Phenobarbital–lidocaine	6 (3%)	6 (2%)	5 (2%)	2 (1%)	4 (1%)	0.1544
Phenytoin–phenobarbital	8 (3%)	8 (3%)	2 (1%)	2 (1%)	1 (0.4%)	0.0008

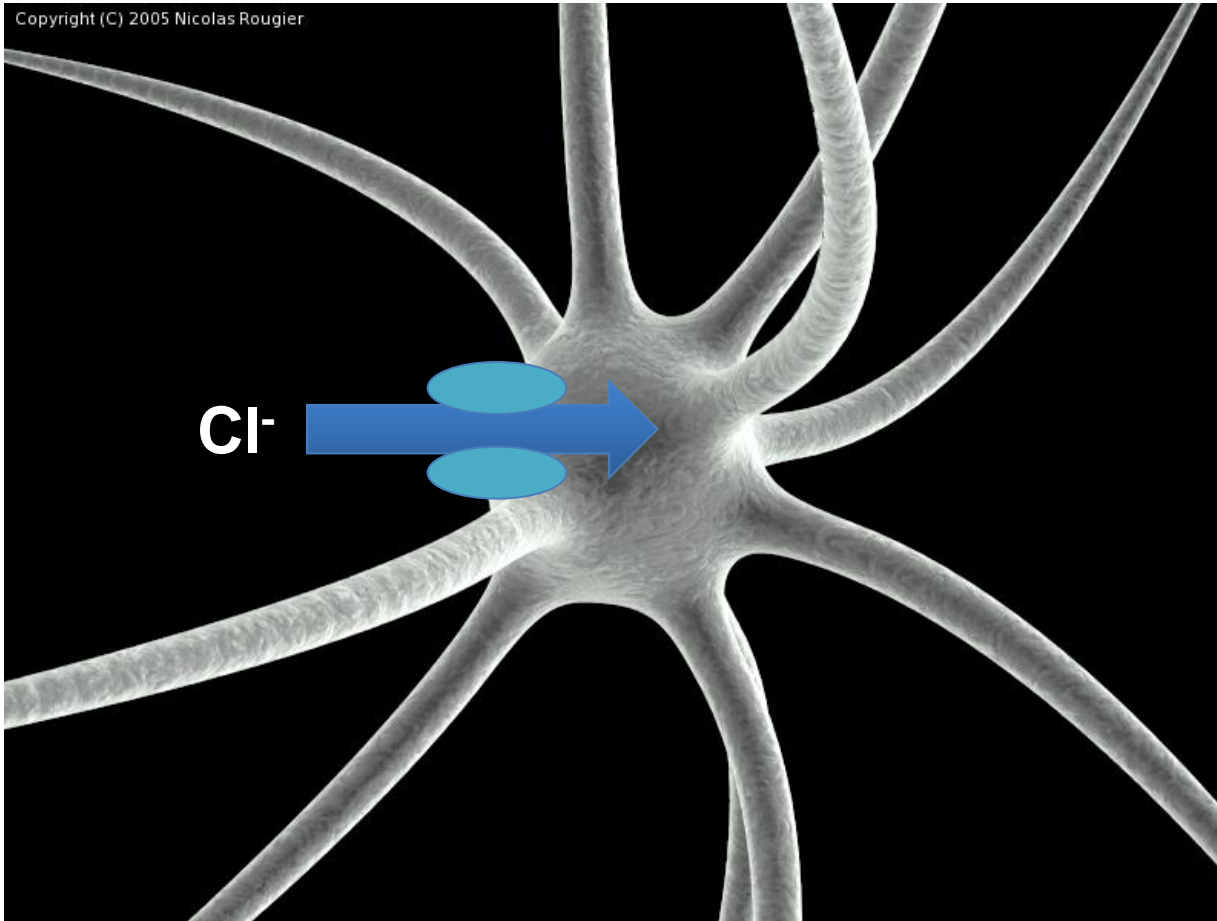


Phenobarbital

- Overall, seizure-reduction efficacy of 43%¹
 - In combination with PHT, 60%
- Inconsistent practices re: loading vs maintenance
 - Continue through acute period
 - 23% surveyed “always” continue maintenance²
- Pros: familiar, has some evidence basis, long half-life
- Cons: respiratory depression, sedation, long half-life

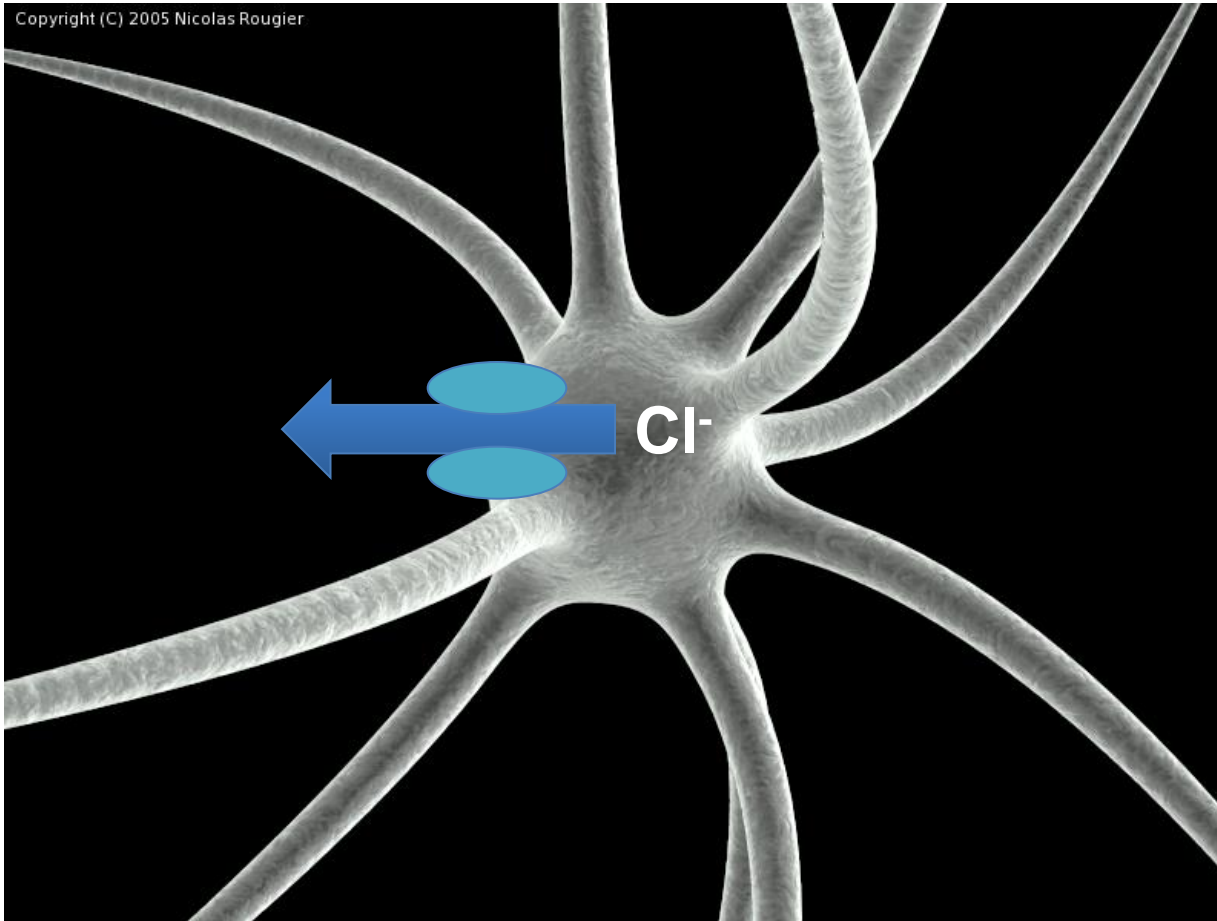
1. Painter MJ. NEJM 1999.
2. Guillet R. Pediatrics 2008.

GABA Receptors



- Normally, GABA gated chloride channels open to allow Cl^- to enter the neuron
- This hyperpolarizes the cell, creating an inhibitory effect

GABA Receptors



- Neonatal neurons are more excitable
- Potassium/Chloride transporters have not yet matured
- Excess Cl⁻ inside immature neurons
- When GABA-activated Cl⁻ open, cell is depolarized
- GABA has a paradoxical excitatory effect in immature neurons, especially in preterms

Phenytoin

- Overall, seizure-reduction efficacy of 45%¹
 - In combination with PB, 60%
- Loading vs maintenance dosing
 - Maintenance dosing difficult due to pharmacokinetics, drug interactions.
- Fosphenytoin
 - Much more expensive (20x)
 - Fewer infusion-related complications
- Pros: Na⁺ channel blocker, quick infusion
- Cons: hypotension, bradycardia, narrow therapeutic range

1. Painter MJ. NEJM 1999.

Levetiracetam

- Case series show safety & tolerability among neonates at 10-50 mg/kg/day^{1,2,3}
- Retrospective series suggest efficacy
- Randomized trial currently underway
- Pros: much less sedating, renal metabolism
- Cons: limited data on efficacy, larger volume and slower infusion rate

1. Furwentsches A. Seizure 2010.
2. Ledet DS. Euro J Paed Neurol 2010.
3. Ramantani G. Euro J Paed Neurol 2011.

Benzodiazepines

- At some centers, preferred second-line drug.¹
- Some evidence of efficacy in seizures refractory to PB + PHT²
- Loading vs maintenance dosing
- Midazolam
 - 15-60 microgram/kg load
 - Infusion 150 up to 300 microgram/kg/hour
 - Tighter titrations 1→18 micrograms/kg/min also used
 - Paradoxical myoclonus has been reported
- Pros: easy to titrate, familiar agents
- Cons: sedation, still acting on GABA-R

1. Vento M. Acta Paediatrica 2010.
2. Castro Conde JR. Neurology 2005.

My Approach

Phenobarbital

- 20 mg/kg load x2 (to level >40*)
- 4-6 mg/kg/d maintenance

Phenytoin (or lidocaine?)

- 20 mg/kg load x1 (to level 15-20*)
- 5-10 mg/kg/d maintenance div TID

Levetiracetam

- 40-60 mg/kg load x1-2
- 40-60 mg/kg/day maintenance div TID

~15-20 minutes between steps

*Post-load levels 1-2 hours after

Summary

- There is evidence to suggest neonatal seizures can be harmful, even beyond underlying causes
- Neonatal seizures cannot be reliably diagnosed by clinical observation; cEEG monitoring is the gold standard for diagnosis
- Babies with brain injury (HIE, stroke) are at high risk for seizures
- Current drugs are imperfect for neonatal seizures; trials of new agents are ongoing

Questions?