Refractory and Super Status Epilepticus: What do we do???

ANUJ JAYAKAR MD

DIRECTOR OF NEUROCRITICAL CARE

ASSOCIATE PROGRAM DIRECTOR, CLINICAL NEUROPHYSIOLOGY FELLOWSHIP

NICKLAUS CHILDREN'S HOSPITAL

MIAMI, FL

epilepsy ALLIANCE FLORIDA

THE POWER OF LOCAL

Nicklaus Children's Hospital

Disclosures

- None

Objectives

- Review the definitions of status epilepticus, refractory status epilepticus, and super-refractory status epilepticus
- Discuss seizure detection strategies including EEG monitoring
- Updates of the current literature on treatment of status epilepticus, refractory status epilepticus, and super refractory status epilepticus
- Brief overview on prognosis
- Review future detection and treatment options

What is Status Epilepticus (SE)??

- Life threatening emergency that requires prompt treatment
- Results from either
  - Failure of mechanisms of seizure termination
  - Initiation of mechanisms which lead to abnormally prolonged seizures
- Can result in neuronal death, injury, and alteration of neuronal networks
- Incidence: 20/100,00
- 3% mortality
- Health care cost of about $4 billion USD per year

Guracharran et al. 2018

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

Trinka E et al. 2015

Refractory and Super Refractory SE

- Refractory SE (RSE): SE that fails to respond to adequately used first and second line AEDs
- Super Refractory SE (SRSE): SE that persists for 24hrs or more after administration of anesthesia, or recurs after its withdrawal
- 10-40% of SE progresses to RSE
- Veterans Affairs Status Epilepticus Trial 1998
  - In adults 55% will respond to first administered therapy
  - 2nd drug only stopped 7%, 3rd drug only 2.3%
  - 23% required non-study drug to stop SE
- No clear evidence to guide therapy with refractory SE
- Goal is to induce "pharmacologic coma" to provide seizure control and/or induce burst suppression
- Associated with long term neurological dysfunction and high mortality (16-43%)

Abend N, 2015
Vasquez A, 2019

Etiology of RSE/SRSE

- Acute symptomatic
  - Infectious or immune encephalitis
  - Traumatic brain injury
  - Ischemic injury
- Remote symptomatic with acute precipitant
  - Past infections
  - Remote HIE
  - Neurodevelopmental condtion/Epilepsy
- Remote symptomatic and progressive conditions
  - Epileptic encephalopathies
  - Metabolic conditions

- Febrile
- NORSE/FIRES

Vasquez, 2019

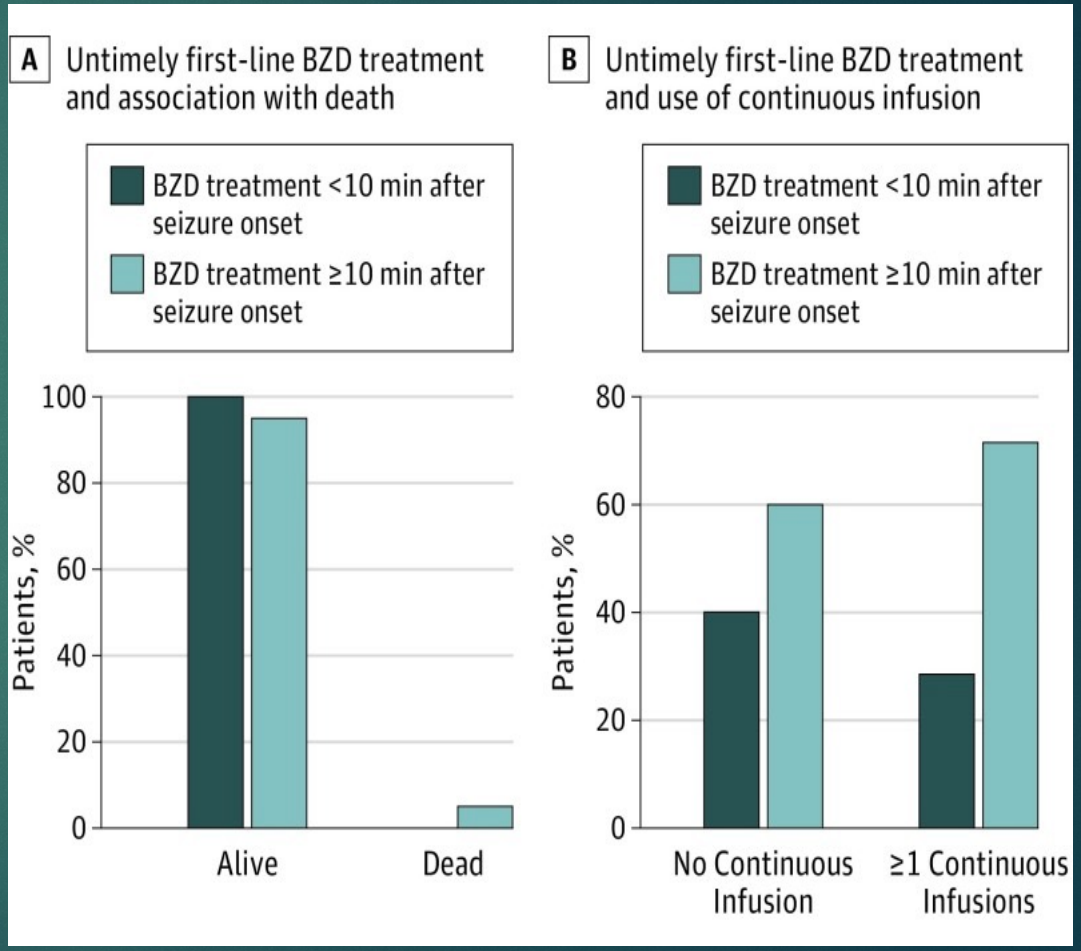
Rapid detection

How to stop prolonged seizures

Rapid Treatment

Importance of early detection

- Treatment delays can lead to longer seizure duration
- Up to 70% of patients receive first line treatment >10 min after seizure onset
  - Higher odds ratio for mortality (AOR 11)
  - Higher odds ratio for requiring continuous anesthetic infusion (AOR 1.8)
  - Longer period of convulsive seizure duration
  - More frequent hypotension



Gainza et al. 2018

Who is at risk for electrographic SE

- Younger age
- Convulsive seizures or SE prior initiation of EEG monitoring or with >10 min of altered mental status after
- Encephalopathy after cardiac arrest
- Traumatic brain injury
- Intracranial hemorrhage
- Presence of interictal epileptiform discharges or periodic discharges on EEG

Role of EEG

- Can measure brain's electrical activity
- Can be recorded at bedside
- Good spatial and temporal resolution
- Continous EEG (cEEG)
  - 10-40% of children with critical illness who undergo cEEG monitoring have electrographic seizures
  - 1/3 of these children meet criteria for status epilepticus
  - 1/3 of children will have electrographic-only seizures
- Limitations: availability of resources
  - Monitoring machines
  - Technicians
  - Trained specialists for interpretation

Herman S, et al. 2015.
Abend N, 2015

Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I: Indications

Susan T. Herman, Nicholas S. Abend,† Thomas P. Bleck,‡ Kevin E. Chapman,§ Frank W. Drislane,* Ronald G. Emerson,‖ Elizabeth E. Gerard,¶ Cecil D. Hahn,# Aatif M. Husain,**†† Peter W. Kaplan,‡‡ Suzette M. LaRoche,§§ Marc R. Nuwer,‖‖ Mark Quigg,¶¶ James J. Riviello,## Sarah E. Schmitt,*** Liberty A. Simmons,††† Tammy N. Tsuchida,‡‡‡ and Lawrence J. Hirsch§§§*

Identify non-convulsive seizures and NCSE

- Persistently abnormal mental status following GCSE or other clinically evident seizures
  - 33% of children after GSCE had ongoing electrographic seizures
  - If no improvement after 10 min following last seizures
- Acute supratentorial brain injury with altered mental status
  - <18yo at higher risk for NCSE than adults
  - Neonates and infants at higher risk than older children
- Fluctuating mental status or unexplained alteration of mental status without brain injury
- Periodic discharges on routine EEG
- Requirement for pharmacologic sedation or paralysis and risk for seizures
  - Hypothermia
  - ECMO
- Clinical paroxysmal events suspected to be seizures

Sanchez Fernandez, et al. 2014
Herman S et al, 2015

TABLE 1. Common Neurological, Medical, and Surgical Conditions Associated With High Likelihood of Recording Seizures on Critical Care Continuous EEG

	Adults	Children	References
Following convulsive status epilepticus	48%	26%–57%	Abend et al., 2011b, 2013b; DeLorenzo et al., 1998; Sanchez Fernandez et al., 2014; Tay et al., 2006; Williams et al., 2011
Aneurysmal subarachnoid hemorrhage	Any seizure: 10%–19% NCSE: 3%–13%		Claassen et al., 2004a, 2006, 2014; Dennis et al., 2002; Little et al., 2007; O'Connor et al., 2014; Westover et al., 2014
Intraparenchymal hemorrhage	16%–23%	11%–100%	Claassen et al., 2007; Greiner et al., 2012; Jette et al., 2006; Kirkham et al., 2012; Kurtz et al., 2014; McCoy et al., 2011; Payne et al., 2014; Saengpattrachai et al., 2006; Tay et al., 2006; Vespa et al., 2003; Westover et al., 2014
Moderate-to-severe traumatic brain injury	18%–33%	14%–70%	Abend et al., 2011b, 2013b; Arndt et al., 2013; Claassen et al., 2004a; Hasbani et al., 2013; Jette et al., 2006; Payne et al., 2014; Ronne-Engstrom and Winkler, 2006; Sanchez et al., 2013a; Schreiber et al., 2012; Vespa et al., 1999b; Williams et al., 2011
Central nervous system infections	10%–33%	16%–100%	Abend et al., 2011b, 2013b; Carrera et al., 2008; Claassen et al., 2004a; Gwer et al., 2012; Jette et al., 2006; Payne et al., 2014; Saengpattrachai et al., 2006; Schreiber et al., 2012; Tay et al., 2006; Westover et al., 2014; Williams et al., 2011

Recent neurosurgical procedures	23%	71%	Claassen et al., 2004a; Payne et al., 2014; Westover et al., 2014
Brain tumors	Any seizure: 23–37% NCSE: 9–12%	19%–66%	Abend et al., 2011b, 2013b; Greiner et al., 2012; Jette et al., 2006; Kirkham et al., 2012; Marcuse et al., 2014; Westover et al., 2014
Acute ischemic stroke	6%–27%	20%–71%	Abend et al., 2011b; Claassen et al., 2004a; Greiner et al., 2012; Jette et al., 2006; Kirkham et al., 2012; Kurtz et al., 2014; McCoy et al., 2011; Payne et al., 2014; Saengpattrachai et al., 2006; Sanchez et al., 2013b; Vespa et al., 2003; Westover et al., 2014
Hypoxic–ischemic injury following cardiac or respiratory arrest, with or without therapeutic hypothermia	10%–59%	16%–79%	Abend et al., 2009, 2011b, 2013b; Claassen et al., 2004a; Crepeau et al., 2013; Jette et al., 2006; Kawai et al., 2011; Knight et al., 2013; Legriel et al., 2013; Mani et al., 2012; Payne et al., 2014; Rittenberger et al., 2012; Sadaka et al., 2014; Sanchez et al., 2013a; Tay et al., 2006; Westover et al., 2014; Williams et al., 2011
Sepsis-associated encephalopathy	32%	58%	Abend et al., 2013a; Oddo et al., 2009
Extracorporeal membrane oxygenation		21%	Piantino et al., 2013
Epilepsy related	33%–39%	11%–71%	Abend et al., 2011b, 2013b; Claassen et al., 2004a; Hyllienmark and Amark, 2007; Jette et al., 2006; McCoy et al., 2011; Saengpattrachai et al., 2006; Tay et al., 2006; Westover et al., 2014; McCoy et al., 2011

NCSE, nonconvulsive status epilepticus.

Timing and Duration of cEEG

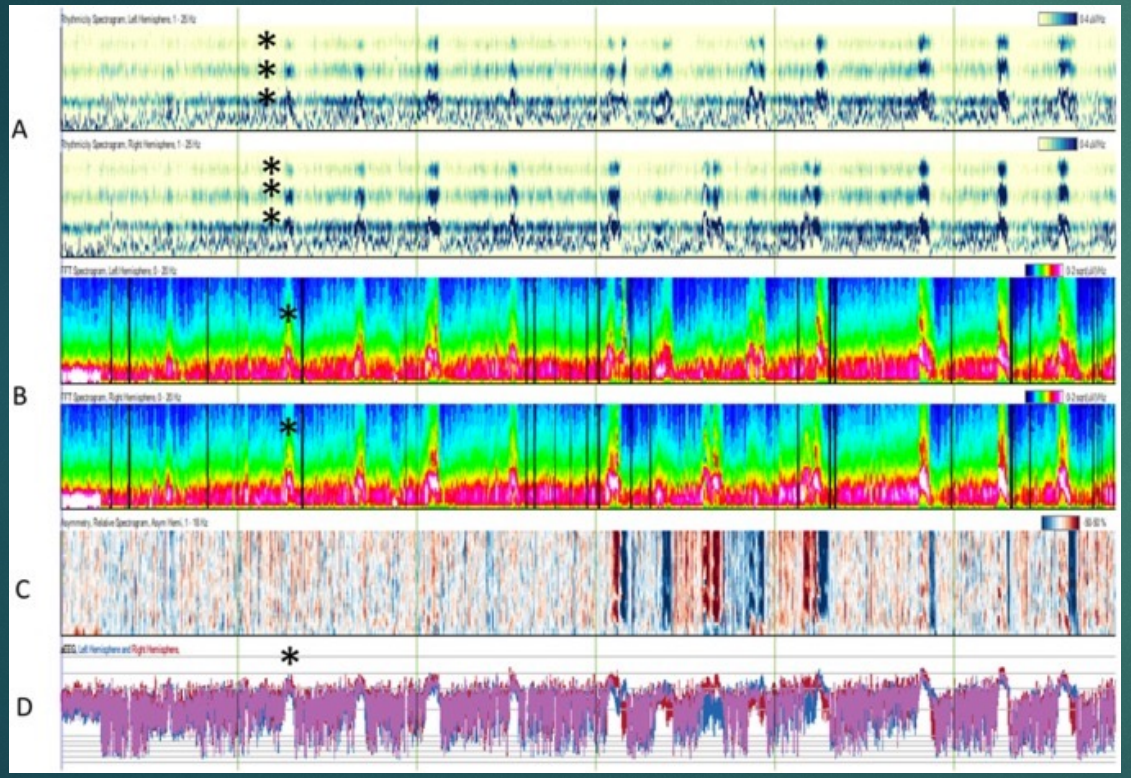
- Initiated as soon as possible
- Length depends on clinical scenario
- Most recommend at minimum 24hrs
- Neonatal seizures
  - Most centers record for duration of protocol and into rewarming
  - Newer data indicates that background activity in 1st 24-48hrs may indicate risks for seizures during remainder of protocol
  - Patients with 1) depressed and undifferentiated or burst suppression with higher OR

Clinical Outcomes	Degree of Encephalopathy (Day 2)		
	Normal/Mild	Moderate/Markedly Abnormal	P-value*
Had Seizure, n (%)			
Yes	1 (2%)	14 (32%)	< 0.001
No	17 (39%)	12 (27%)	
*p-value calculated from Fisher's Exact Test or Chi-Squared Test of Association			

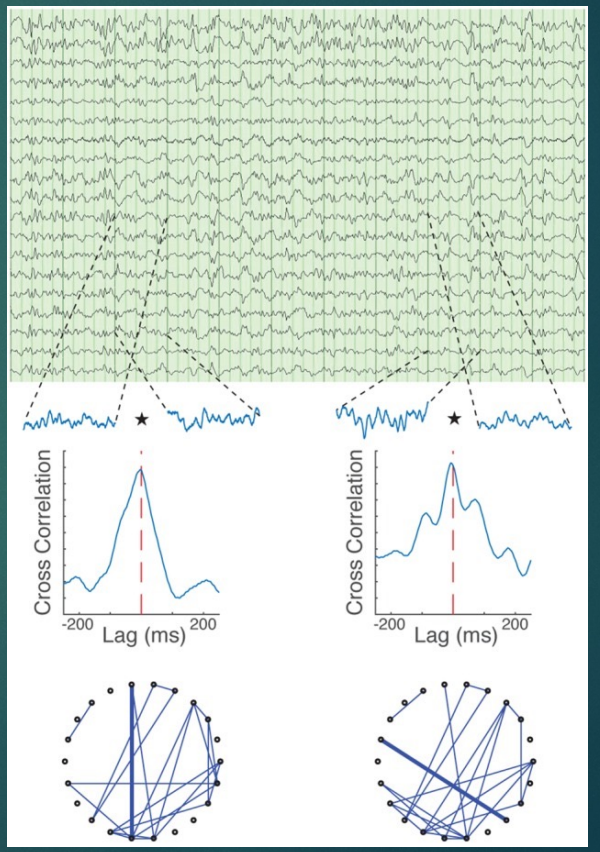
Glass et al. 2014
Fajardo M et al. 2018
Sansevere et al 2019
Benedetti e al, 2020

Beyond EEG!!!!

Quantative EEG

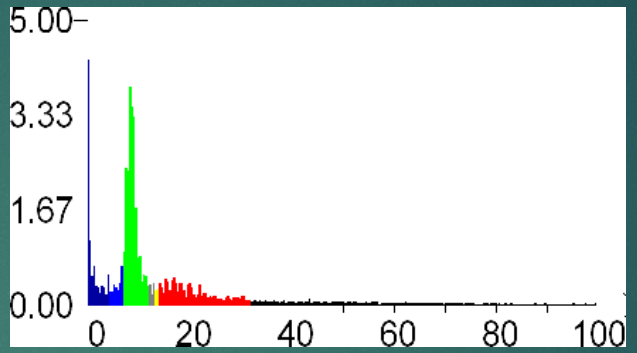


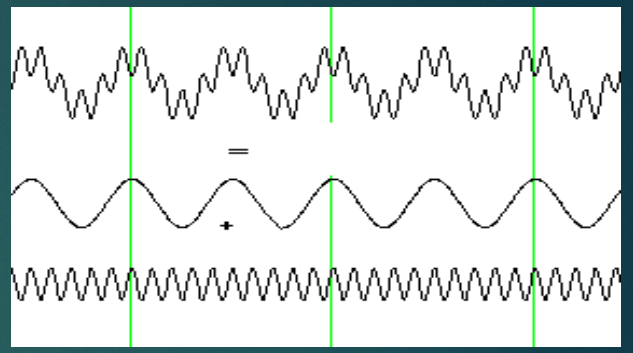
EEG Connectivity

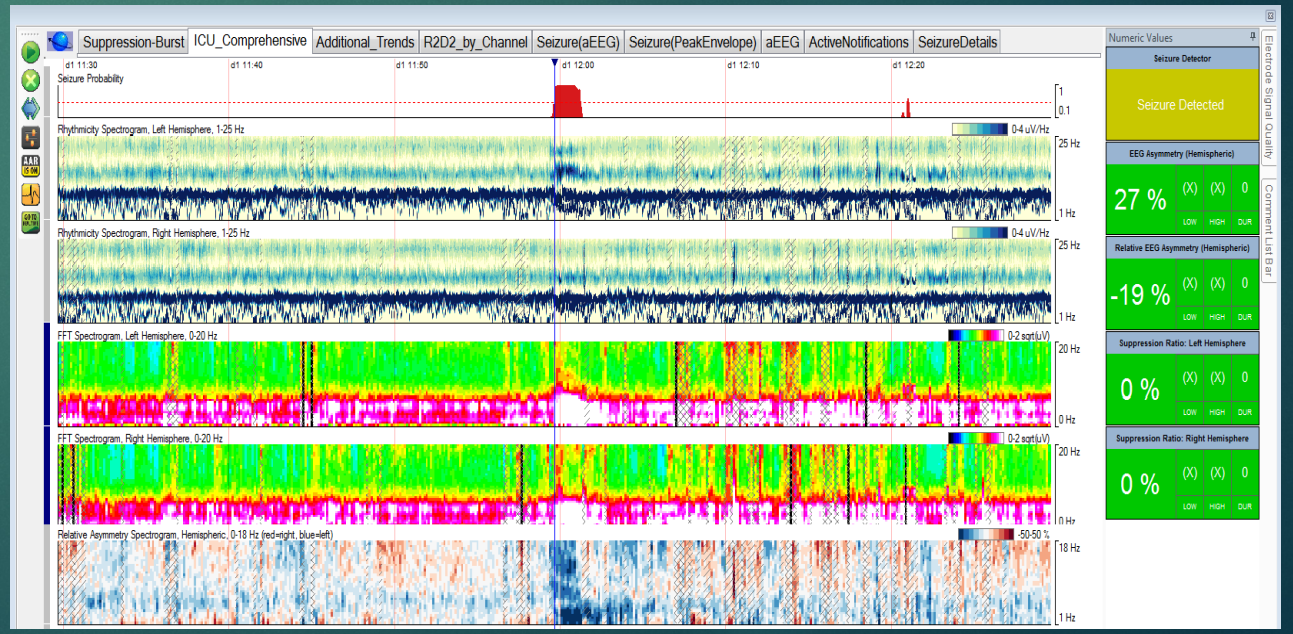


Utilization of Amplitude Integrated EEG

- A special software makes spectral analysis to display the different trends like aEEG, rhythmicity, power, asymmetry trends
- Review at a glance (minutes-hours instead of seconds)
- Rapid recognition of nonconvulsive seizures
- Better timing of treatment
- Provides a quick overview of seizure location, frequency and duration
- Reveals subtle background asymmetry, changes in state, reactivity and rhythmic or periodic patterns







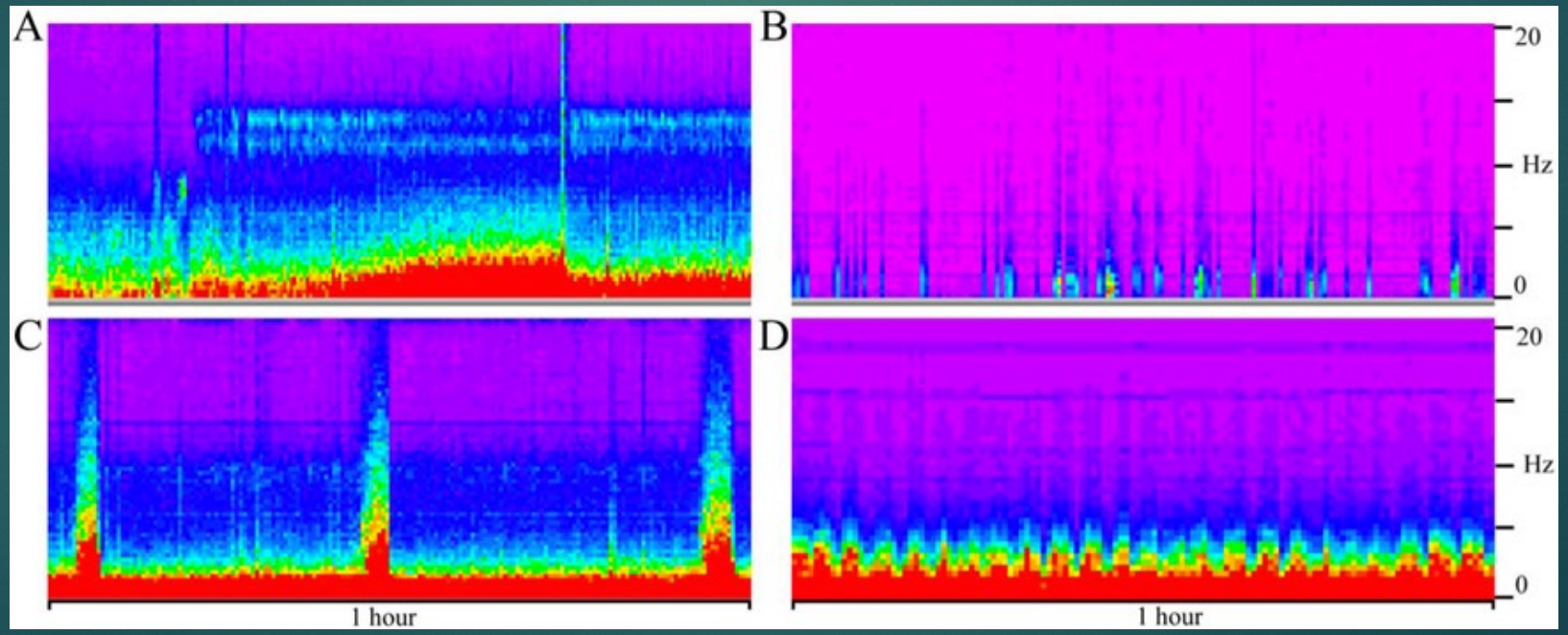
Bedside Management of SE using QEEG

- QEEG utilized in numerous ICUs across the country
- Lack of training a common barrier
- How QEEG is utilized is still variable
- Ganesan et al → critical care providers can be trained to utilize QEEG for seizure detection
- Development of Pediatric Quantitative EEG Strategic Taskforce (PEDS-QUEST)

Benedetti G, et al 2023
Ganesan SL et al, 2018

Further use of QEEG

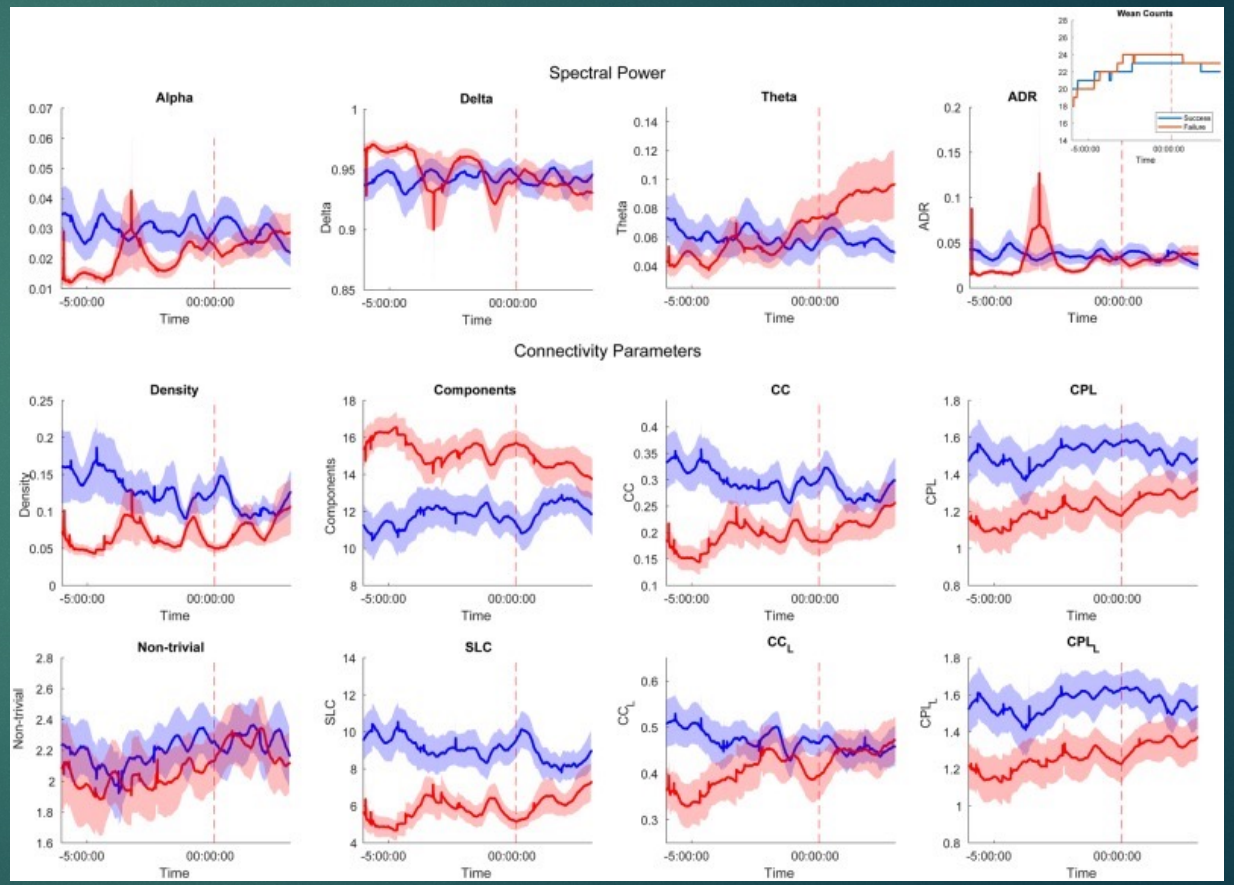
- Macroperiodic oscillations- slow periodic patterns occurring over a longer time scale than periodic discharges
- Associated with seizures in young patients in in TBI



Guerriero et al, 2021

EEG Connectivity and QEEG

- Assessed role of spectral frequency analysis and EEG connectivity in weaning off of sedation in SRSE
- A number of connectivity measures prior to weaning had a predictive capability for wean success
- Pre-wean frequency was less consistently successful



Rubin D, et al. 2020

Treatment of SE

Initial Steps

- Stabilize patient
  - **ABC's!!**
  - Monitor vital signs
  - Assess oxygenation
  - Initiate cardiorespiratory monitoring
- Check fingerstick blood glucose
- Obtain IV access
- Chem, CBC, tox screen, AED levels

Recommended Workup for RSE/SRSE

- Always recommended
  - Dextrose stick
  - Vital signs
  - CT/MRI
  - Serum electrolytes including Mg and Ca
  - Continuous EEG monitoring

- Known Epilepsy Patient
  - ASM levels
  - Consider CT/MRI
  - Consider Electrolytes
- Febrile patient
  - Consider LP
- Suspected Genetic Condition
  - Genetics consultation
  - Tiered genetic testing
- Toxicology

- Suspected non-infectious encephalitis
  - CRP, ESR
  - Auto-antibodies including ANA, anti-dsDNA, ANCA, APS & ENA panel
  - Serum anti-neuronal antibodies including anti-NMDAR, –AMPA & –VGKC, –GABA
  - Lumbar puncture with oligoclonal bands, and CSF anti-neuronal antibodies
  - Paraneoplastic work up if applicable

Vasquez A, 2019

American Epilepsy Society Guideline

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

Tracy Glauser, MD,[1] Shlomo Shinnar, MD, PhD,[2] David Gloss, MD,[3] Brian Alldredge, PharmD,[4] Ravindra Arya, MD, DM,[1] Jacquelyn Bainbridge, PharmD,[5] Mary Bare, MSPH, RN[1], Thomas Bleck, MD,[6] W. Edwin Dodson, MD,[7] Lisa Garrity, PharmD,[8] Andy Jagoda, MD,[9] Daniel Lowenstein, MD,[10] John Pellock, MD,[11] James Riviello, MD,[12] Edward Sloan, MD, MPH,[13] David M. Treiman, MD[14]

Time Line

Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics

0-5 min
Stabilization
phase

1. Stabilize patient (airway, breathing, circulation, disability - neurologic exam)
2. Time seizure from its onset, monitor vital signs
3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed
4. Initiate ECG monitoring
5. Collect finger stick blood glucose. If glucose < 60 mg/dl then
   Adults: 100 mg thiamine IV then 50 ml D50W IV
   Children ≥ 2 years: 2 ml/kg D25W IV Children < 2 years: 4 ml/kg D12.5W
6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels

Does Seizure continue?

Yes

No

5-20 min
Initial therapy
phase

A benzodiazepine is the initial therapy of choice (Level A):

Choose one of the following 3 equivalent first line options with dosing and frequency:

- Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR
- Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
- Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)

If none of the 3 options above are available, choose one of the following:

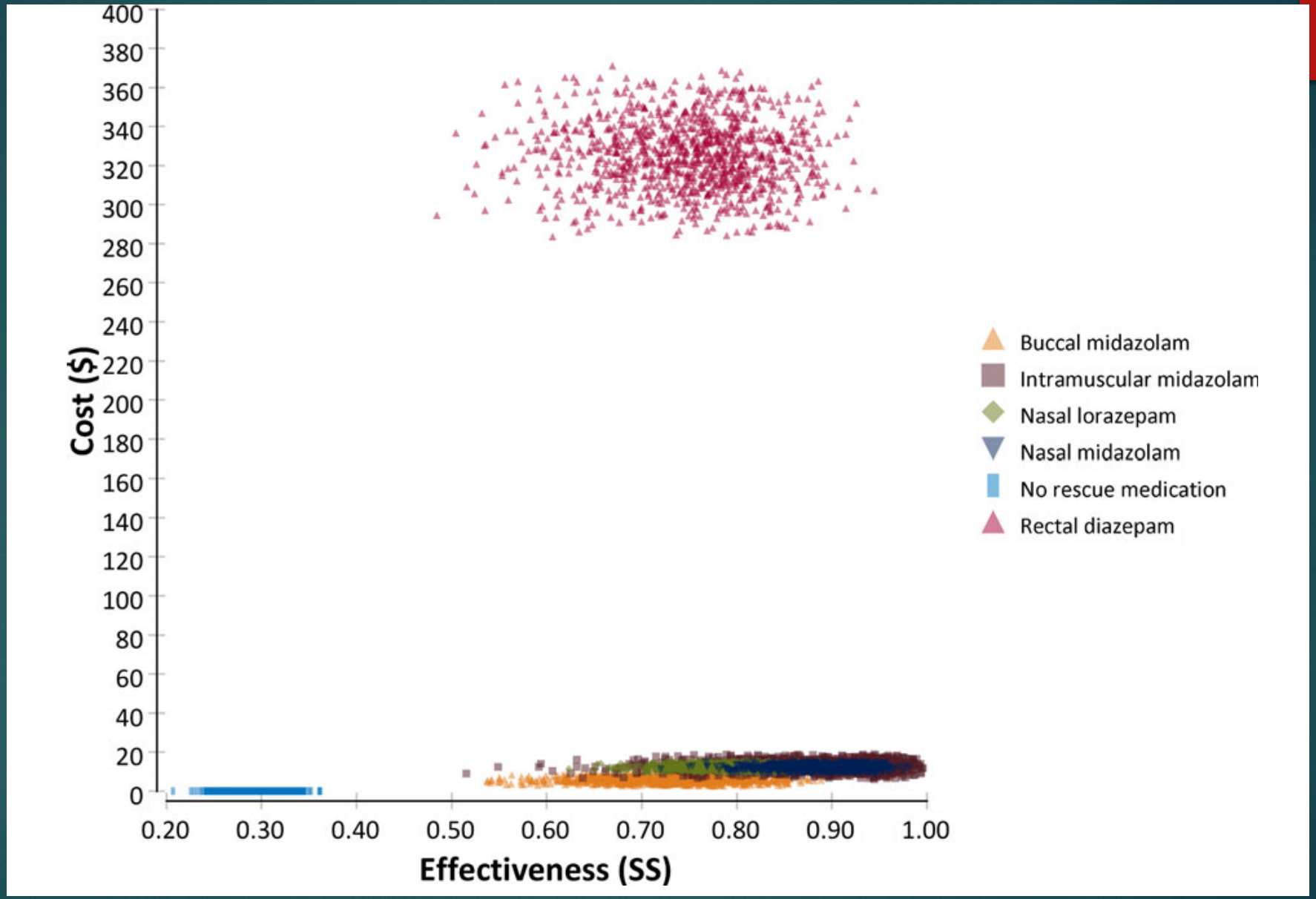
- Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
- Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
- Intranasal midazolam (Level B), buccal midazolam (Level B)

If patient at baseline, then symptomatic medical care

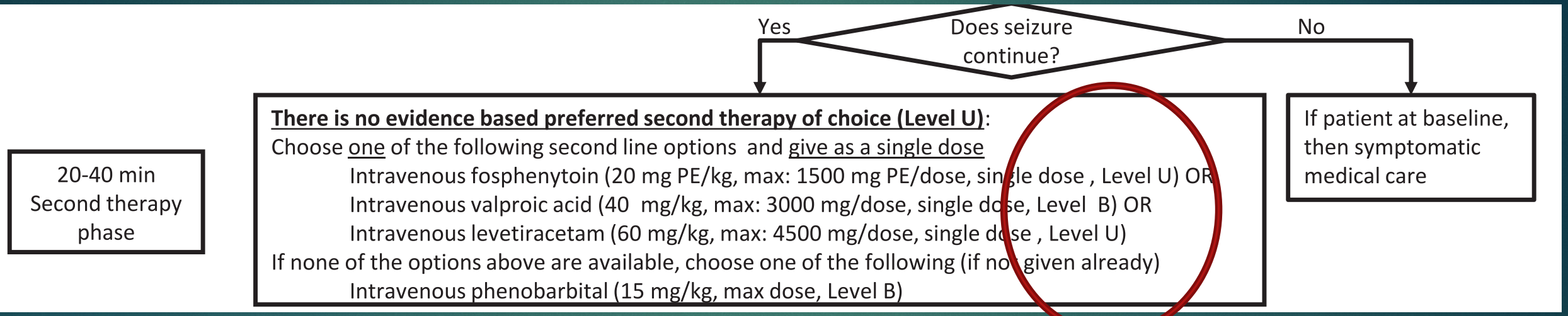
Which Benzodiazepine to Choose?

- Readily available = better!
  - IV lorazepam or diazepam preferred
    - 26 RCTs reviewed
    - No difference between the 2 in terms of efficacy
  - RAMPART Trial 2011: IM midazolam is non-inferior to IV lorazepam
- IM/Inh/buccal midazolam > rectal diazepam
  - More effective in terminating seizures
  - Shorter time to seizure cessation
  - Similar side effect profile
  - Cheaper!

Silbergleit R et al, 2013
Chamberlain JM et al, 2014



Sanchez-Fernandez I et al, 2017


Does seizure continue?
Yes
No
20-40 min
Second therapy phase
There is no evidence based preferred second therapy of choice (Level U):
Choose one of the following second line options and give as a single dose
Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose , Level U) OR
Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose , Level U)
If none of the options above are available, choose one of the following (if not given already)
Intravenous phenobarbital (15 mg/kg, max dose, Level B)
If patient at baseline, then symptomatic medical care

Which AED to choose

- Lack of literature to suggest one AED over another
  - 1 RCT looked at IV valproate vs IV phenobarbital→ similar efficacy but fewer adverse effects with IV valproate
  - 1 RCT comparing IV valproate vs IV fosphenytoin → similar efficacy

Established **S**tatus **E**pilepticus **T**reatment **T**rial (ESETT)

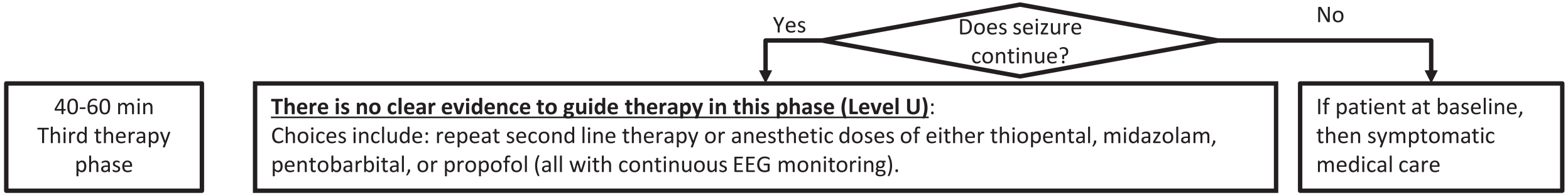
- A multicenter, randomized, blinded, comparative effectiveness study of fosphenytoin, valproic acid, or levetiracetam in the emergency department treatment of patients with benzodiazepine-refractory status epilepticus.
  - No significant difference in seizure cessation
  - Hypotension and intubation rations higher with fosphenytoin
  - Deaths were more frequent

Kapur et al, 2019

Therapy of Established SE: Real world choices

Property/AED	Fosphenytoin	Levetiracetam	Valproic Acid
Popularity of use in the US	Most commonly used (60-65%)	Used often (20-30)	Least often
Ease of administration	Slow	Fast	Fast
Speed of action	Slow administration	Enters brain Slowly, acts slowly	Yes
Action last long	Yes	Yes	Yes
Efficacious in animal models	Least effective	In combination with diazepam	Very effective
Terminates seizures	Partial seizures	Partial and generalized	Partial and generalized
Safe	Hypotension, cardiac arrhythmia.	safe	Safe for acute use

Kapur et al, 2019


Yes
Does seizure continue?
No
40-60 min
Third therapy phase
There is no clear evidence to guide therapy in this phase (Level U):
Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).
If patient at baseline, then symptomatic medical care

Drug	Dosage	Adverse Events	Clinical Considerations
Midazolam	Load: 0.2mg/kg Infusion rate: 0.2-2mg/kg/hr Breakthrough: bolus 0.1-0.2mg/kg, increase rate by 0.2mg/kg/hr	Hypotension, respiratory depression	Prolonged usage may cause tachyphylaxis and drug accumulation
Pentobarbital	Load: 5-15mg/kg Infusion rate: 0.5-10mg/kg/hr Breakthrough: bolus 1-5mg/kg and increase rate by 0.5-1mg/kg/hr	Hypotension, cardiac and respiratory depression, paralytic ileus, infection	Long half-life (15–50 h) Requires mechanical ventilation. Can exacerbate porphyria Hepatic enzyme inducer Drug accumulation with prolonged use
Thiopental	Load: 2–7 mg/kg, Infusion rate: 0.5–5 mg/kg/h Breakthrough SE:1–2 mg/kg bolus, titrate by 0.5–1 mg/kg/h.	Hypotension, cardiac and respiratory depression	Requires mechanical ventilation, titrate infusion rates to EEG burst-suppression
Propofol	Initial loading dose: 1–2 mg/kg Initial infusion rate: 20 mcg/kg/min titrated by 5–10 mcg/kg/min Use with caution with doses > 65 mcg/kg/min Breakthrough SE: Increase infusion rate by 5–10 mcg/kg/min every 5 min	PRIS, hypotension, cardiac and respiratory depression	Requires mechanical ventilation Prolonged infusion of propofol is a relative contraindication in children (due to risk of PRIS) and in patients with metabolic acidosis, mitochondrial disorders or hypertriglyceridemia Reduces ICP Caution with concomitant use of steroid or catecholamine therapy
Ketamine	Load: 0.5–3 mg/kg Infusion rate: 1–10 mg/kg/h	Tachycardia, hypertension, ICP elevation	Relative contraindication in patients with ICP. Ketamine is an enzyme inducer and inhibitor (CYP2C9)
Isoflurane	Concentration 1–5% Titrate to achieve burst-suppression on EEG	Hypotension, atelectasis, paralytic ileus, infection, deep vein thrombosis	High seizure recurrence rate

Vasquez A et al, 2019. Jacobwitz, et al 2022

Immunotherapy

- If autoimmune or inflammatory etiology is suspected
- No good evidence to support specific therapy and timing
- 3 main options
  - Corticosteroids
    - Methylprednisolone 30mg/kg/d or 1g daily
    - Can increase risk for hypertension and infection
  - IVIG: 2g/kg split over 2-4 days
  - PLEX: Typically 5 sessions
- Anakinra (IL1 antaganist)

Marawar et al, 2018

Ketogenic Diet

- No large scale studies to determine effectiveness
- In limited samples, allows patients to be weaned off anesthetics
- Mean time to starting diet: 13 days
- Mean time to achieve ketosis: 2-4.2 days
- 70-90% were able to have seizure resolution and wean off anesthetics
- No set criteria for weaning off anesthetics or determining success of treating SRSE

Farias-Moeller R et al, 2017
Appavu B et al, 2016
Kosoff E et al, 2013

Epilepsy Surgery

J Neurosurg Pediatr. 2013 Oct;12(4):360-6. doi: 10.3171/2013.7.PEDS1388. Epub 2013 Aug 23.

Surgical treatment of refractory status epilepticus in children: clinical article.

Bhatia S[1], Ahmad F, Miller I, Ragheb J, Morrison G, Jayakar P, Duchowny M.

- 15 patients from 1990-2012
- Mean preoperative seizure duration was 8 weeks
- Ictal SPECT and PET used for further localization
- Surgical intervention controlled seizures in all patient and facilitated transfer out of the ICU
- No operative mortality

Alternative Therapies

- Alternative AED options
  - Lacosamide: 40-60% efficacy with low toxicity
    - TRENDS trial 2018: IV lacosamide non-inferior to IV fosphenytoin
  - Perampanel: AMPA receptor blocker
  - Brivaracetam: 30% efficacy with low side effects
- Neurosteroids
  - Allopregnanalone (aka brenaxalone)
    - Phase I/II trial showed 77% efficacy
    - Phase 3 trial showed no benefit when compared to placebo
  - Ganaxalone (ongoing study)
- Therapeutic hypothermia
- Neurostimuilation
  - Transmagnetic stimulation- 71% of focal motor SE had seizure control
  - Vagal nerve stimulation
  - Electroconvulsive therapy

Hussain AM et al. 2018

Outcomes

- Mortality: 14-45%
- Underlying etiology primary predictor of outcome
- Longer RSE and non-convulsive RSE have worse outcomes
- Long hospital stays

Vaquez et al, 2021

Rapid Diagnostics

Inflammatory/Infectious Etiologies
- Low threshold to undertake infectious/inflammatory workup
- Autoimmune encephalitis panel
- Consider early immunomodulation

FIRES
- Early usage of Ankinra
- Can consider PLEX

Genetics
- Utilization of rapid and ultra rapid genomics

Outcomes	Diagnostic Result (N=33)	
	Positive (N= 20)	Negative (N=13)
Led to better outcomes for patient and family	**N(%)**	**N(%)**
Yes	19 (95.0)	4 (30.8)
No	1 (5.0)	9 (69.2)
Led to a shorter hospital stay		
Yes	6 (46.2)	0 (0.0)
No	14 (53.8)	13 (100.0)

Jayakar A et al, (in press)

What the future may look like for RSE/SRSE

- More accurately identifying patient populations at risk
- More aggressive early treatment
- Combination AED treatments
  - Mouse models suggest simultaneous AED administration is efficacious
  - Dexmedetomedine plus midazolam stopped SE in a rat model (McCarren HS et al, 2018)
- Larger dosing of initial AED boluses
- Earlier utilization of ketogenic diet, epilepsy surgery, immunomodulatory therapy
- Individualized patient SE plans
- RSE/SRSE centers for specialized management

Summary

- Time is Brain!!!
- Early detection and early management increases the chances of success and minimizes adverse consequences
- Utilize all resources at disposal to assist in detection and treatment
- In RSE and SRSE, move towards alternative treatment options earlier

Special Thanks!!

- Neurocritical care team
- Neurosurgeons
- Neurohospitalists
- Pediatric ICU Team
- Neonatal ICU Team
- Cardiac ICU team
- Emergency Room Team
- Neuroradiology
- Genetics/Metabolism Team
- Ketogenic diet team
- Pediatric Hospitalists
- EEG technologists
- Research staff

Nicklaus Children's Hospital