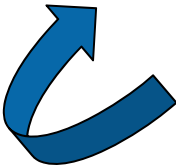
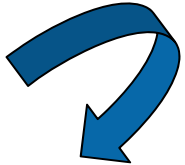




Evidence-based Management of Status Epilepticus.

Stephen Hantus MD
Cleveland Clinic Epilepsy Center

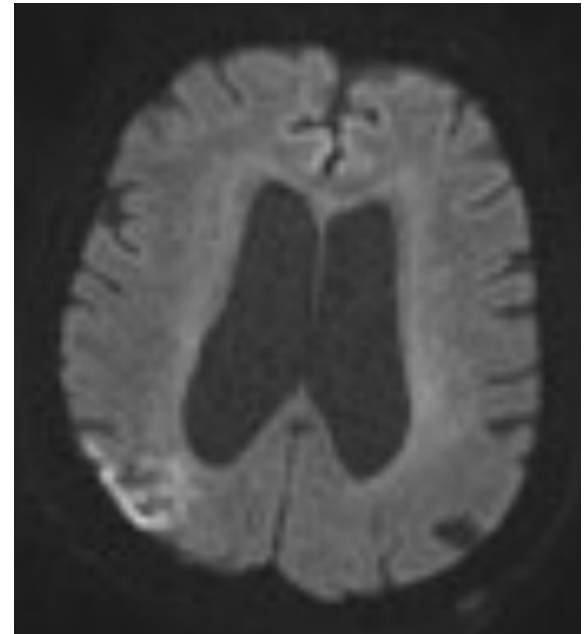
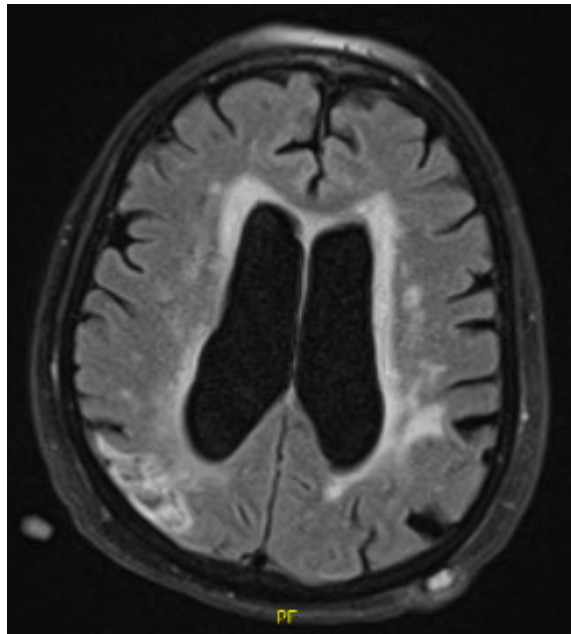
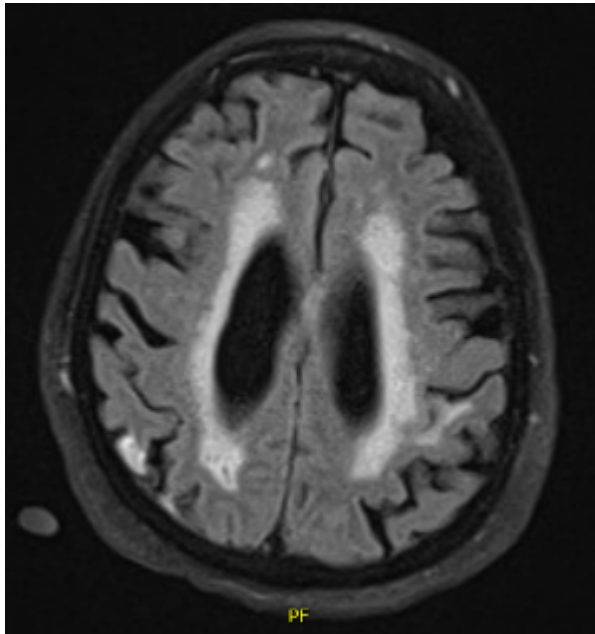
How is Status Epilepticus Identified? A Disease in Transition



Clinical Presentation

- 77 yo female presents with DKA and altered mental status.
- She has a history of a remote right hemispheric stroke 1 year ago, with no apparent residual motor deficit
- After fluids and correction of her DKA, family notes on and off left facial twitching.
- Currently she presents with left facial droop, slurred speech, flaccid left arm paralysis and intermittent left facial twitching.

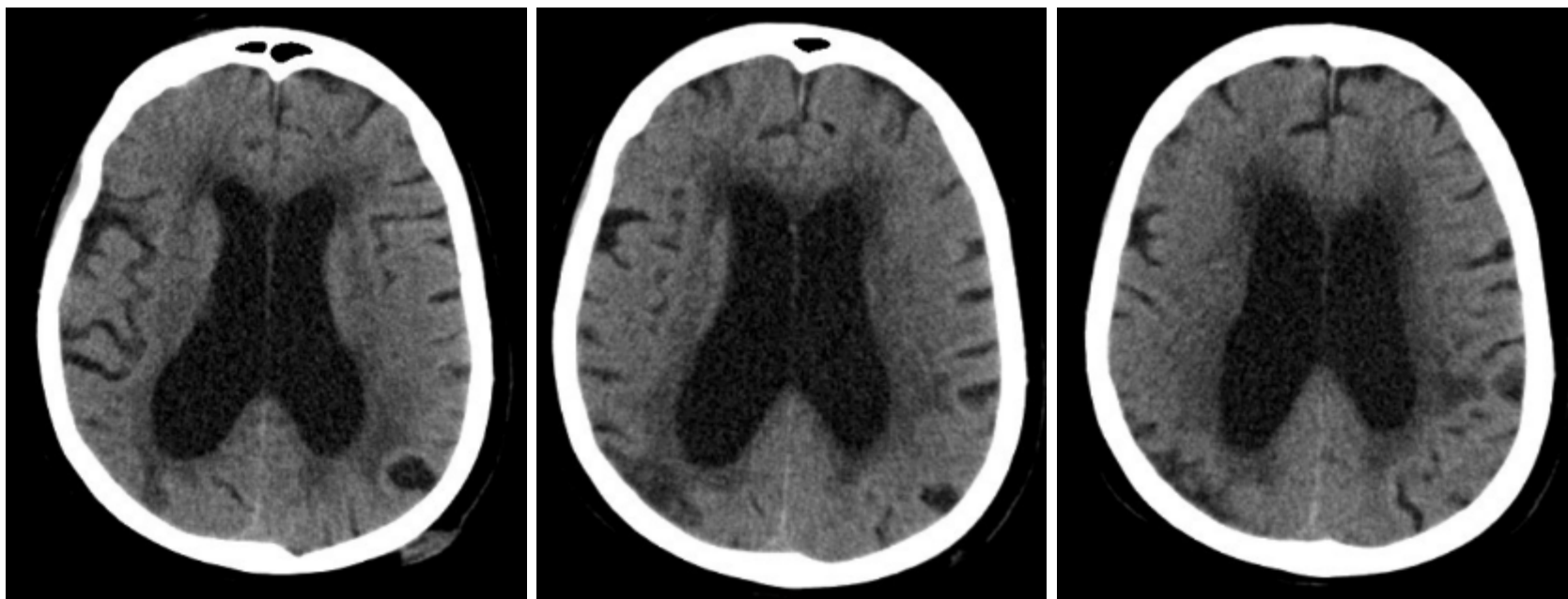
Review of her MRI Brain of Right Parietal Subacute Infarct 1 year ago



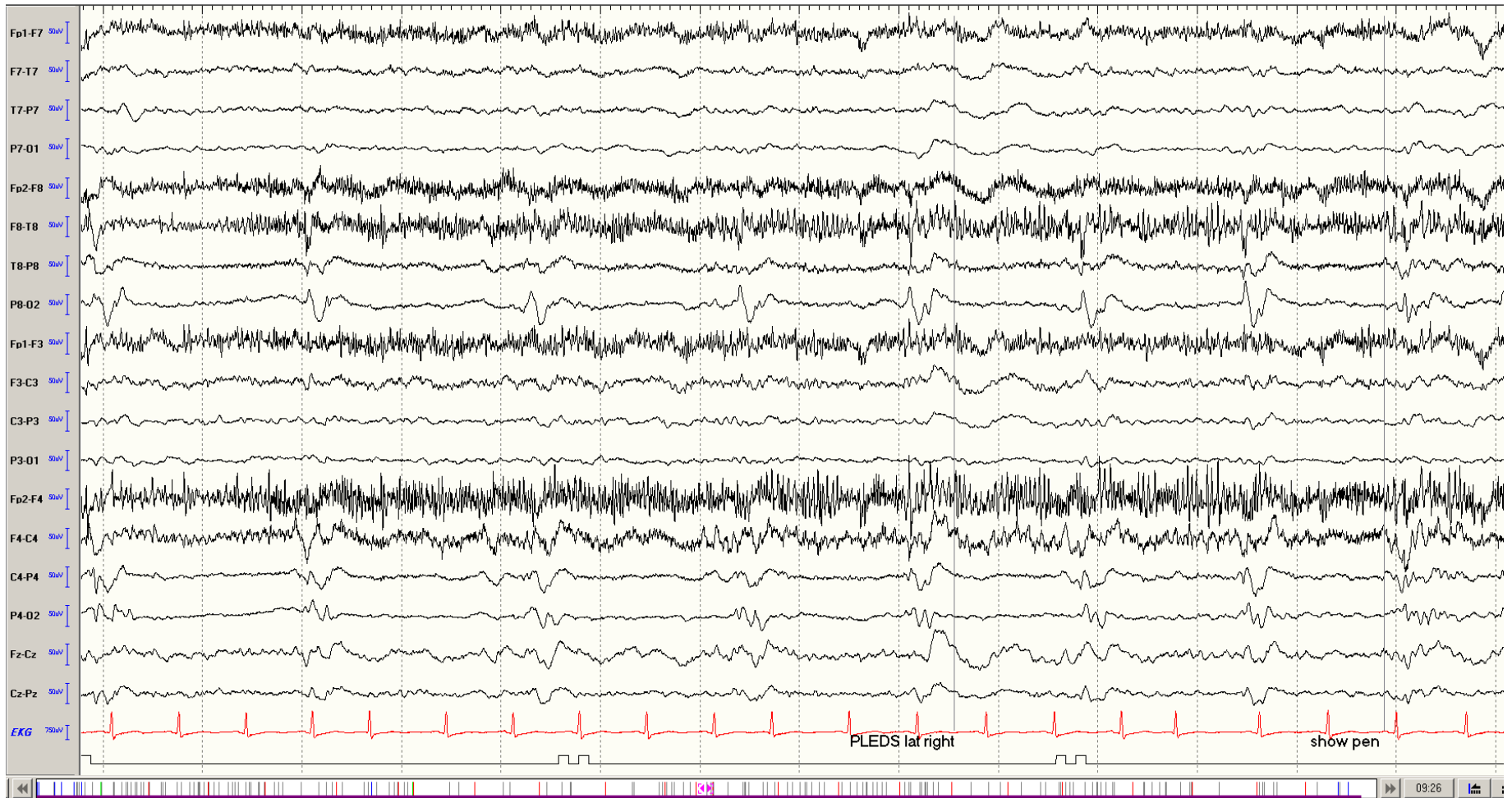
Clinical Course

- Given her flaccid left hemiparesis, Stroke neurology was consulted. Head CT was ordered.
- Ativan 2mg was given with cessation of the twitching of her face, but she became progressively more lethargic
- A routine EEG is ordered

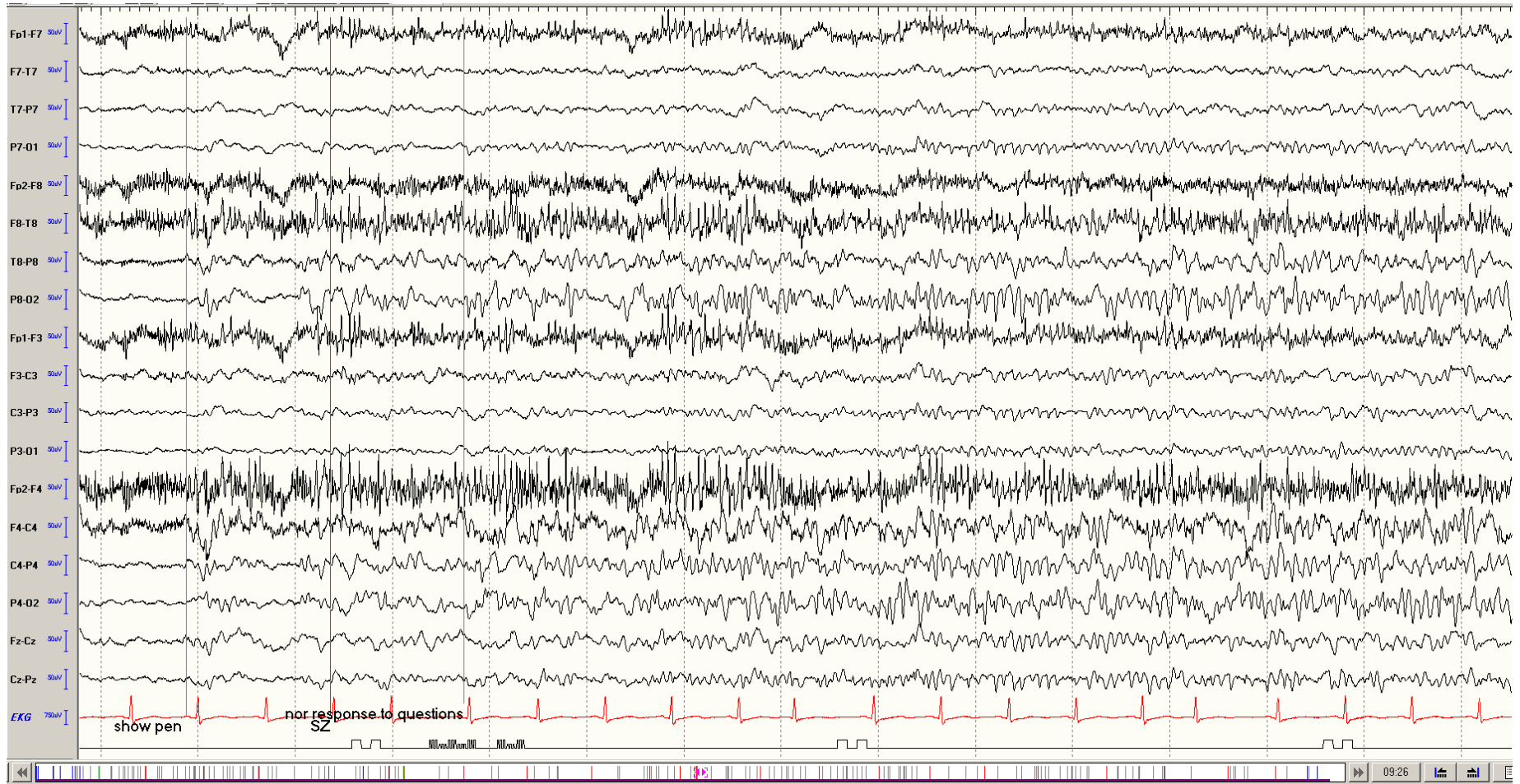
CT Head with Acute Presentation: Remote Infarct



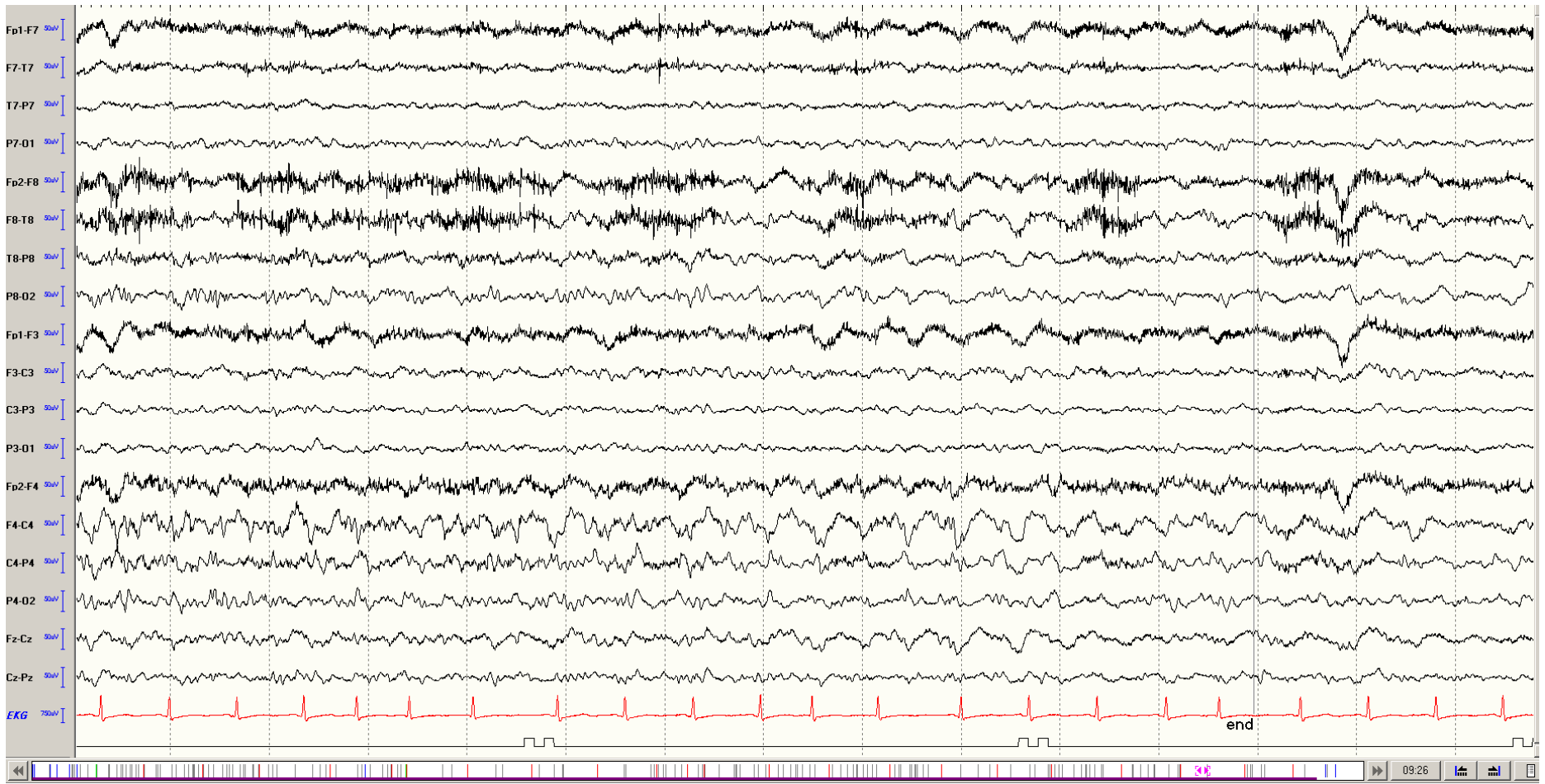
Initial EEG: PLEDs Lateralized Right, expected?



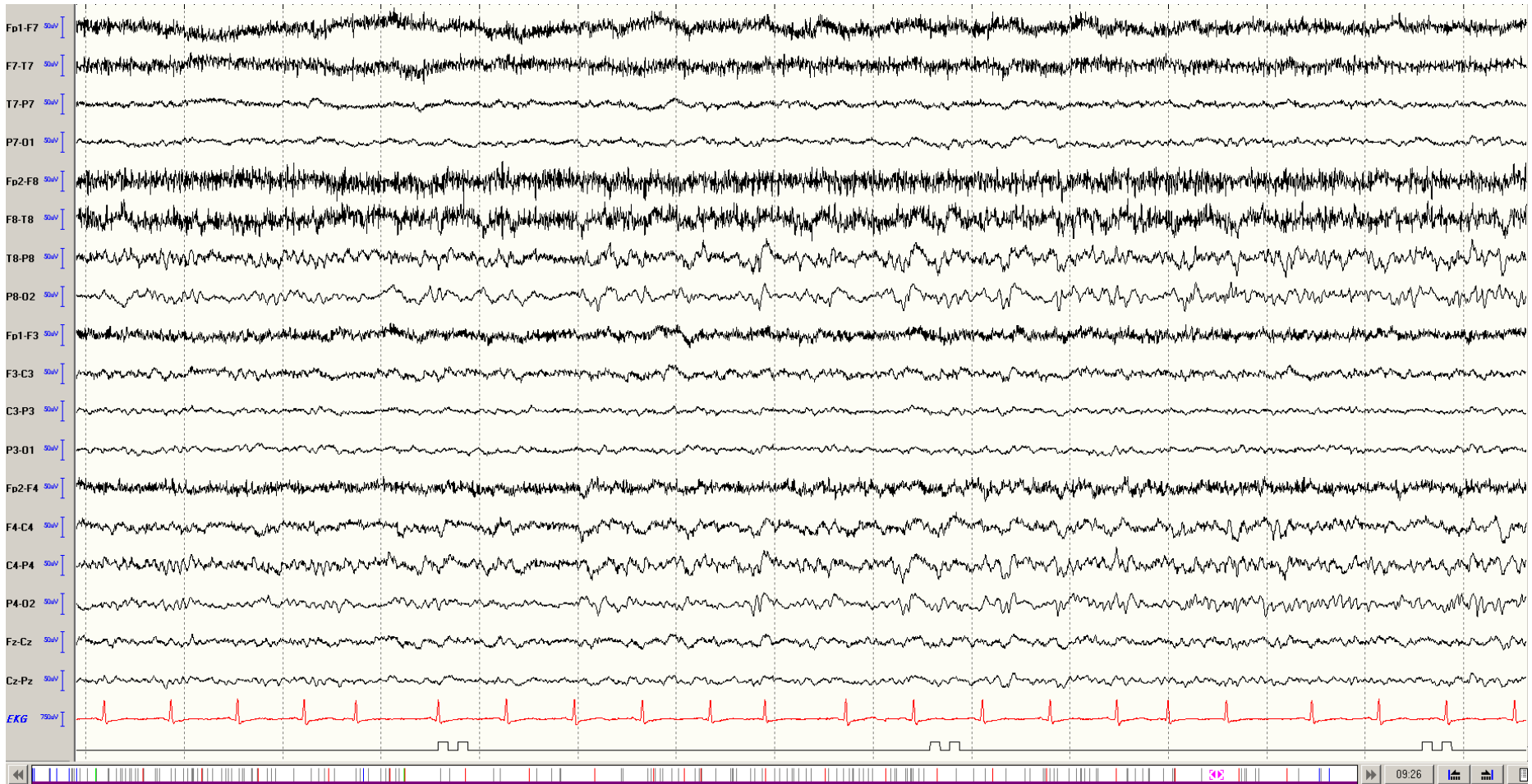
EEG +15 sec: Seizure evolving right hemisphere



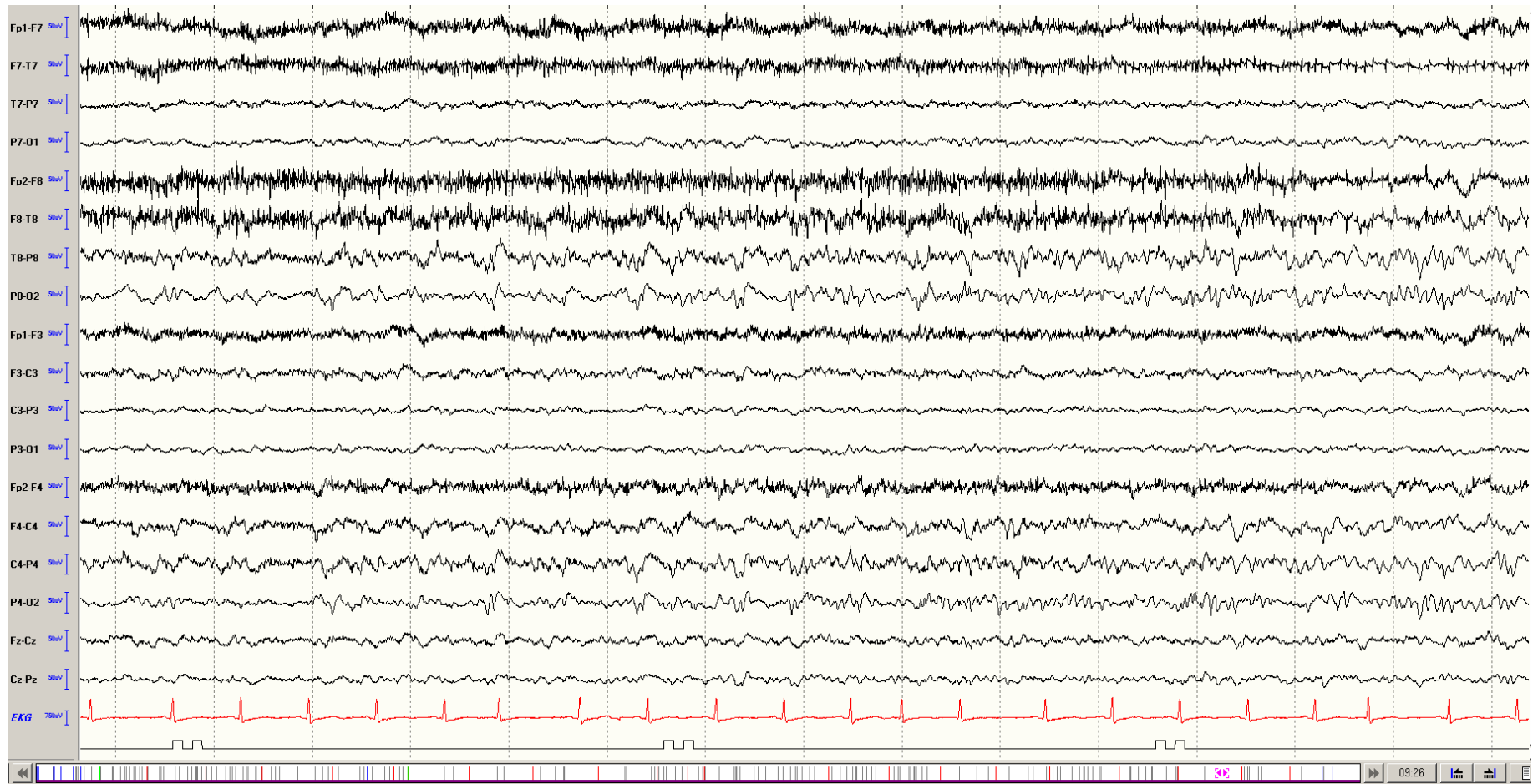
EEG +45 sec: Seizure ends with max slowing right central parietal



EEG +60 sec: Seizure merges with another onset



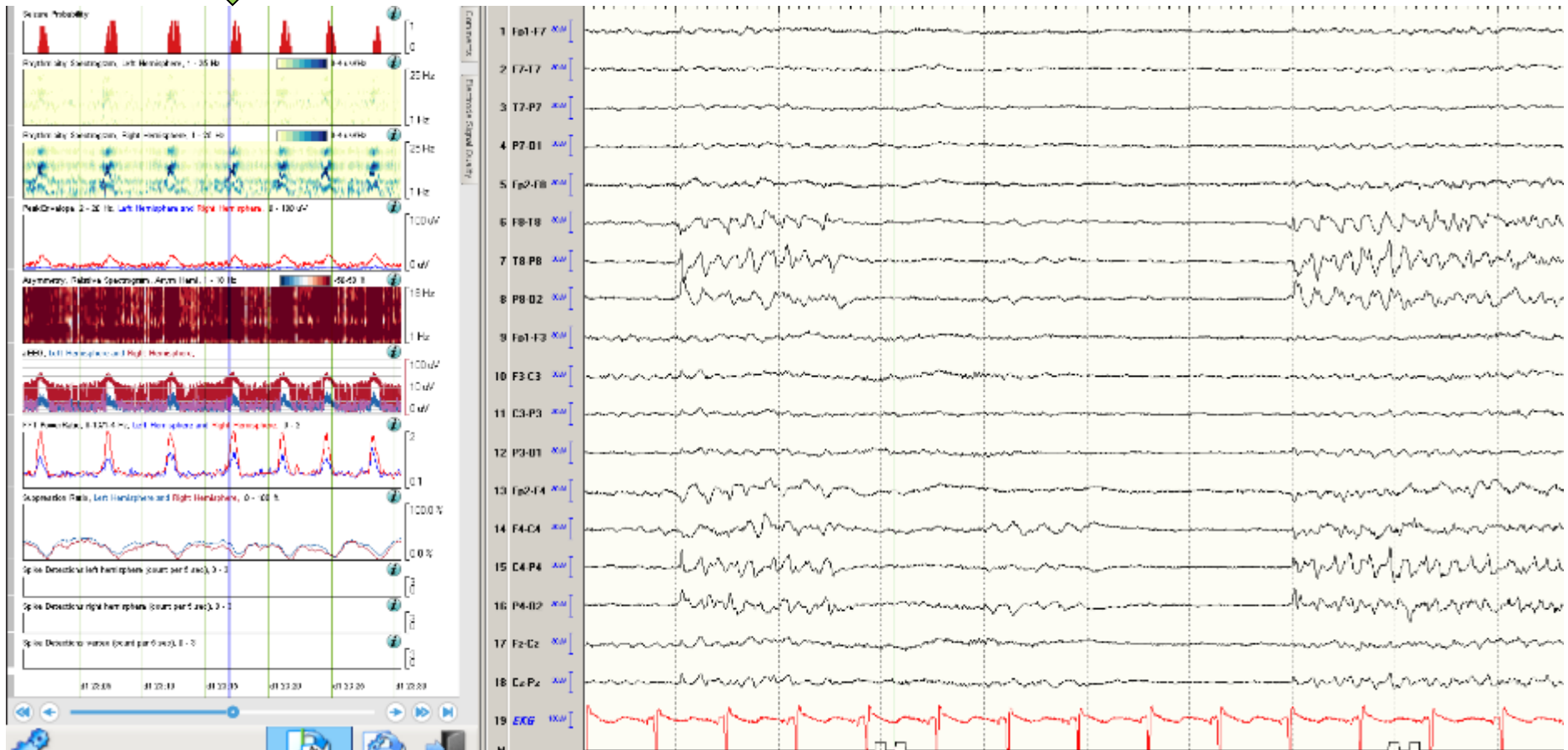
EEG +75 sec: Seizure continues in right hemisphere



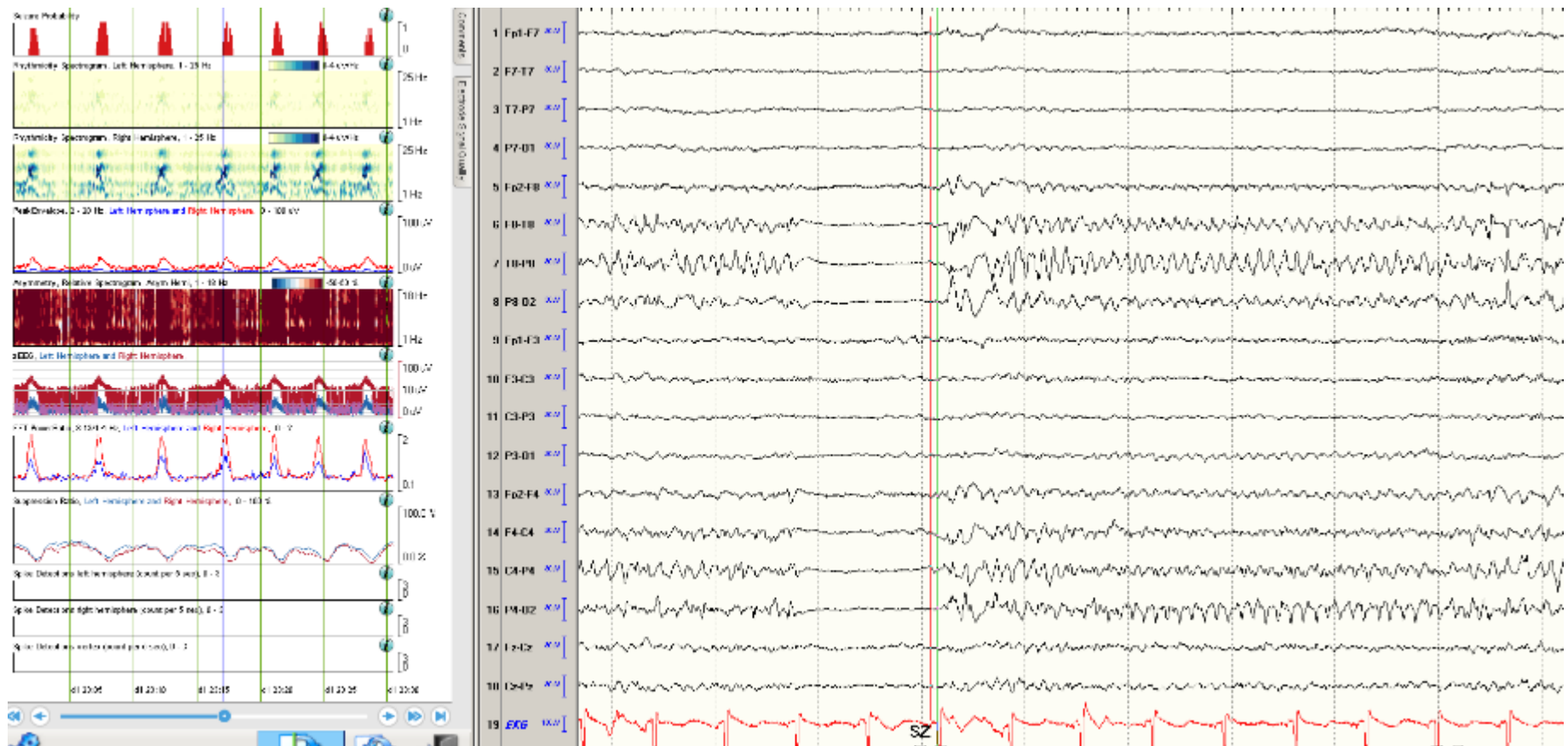
Clinical Course

- After the routine EEG showed status epilepticus, she was transferred for cEEG monitoring in the NICU
- She arrived with an unprotected airway and unresponsive
- Her family is not sure they want aggressive measures and ask to keep her comfortable.
- She is given 4mg of Lorazepam with progressive obtundation

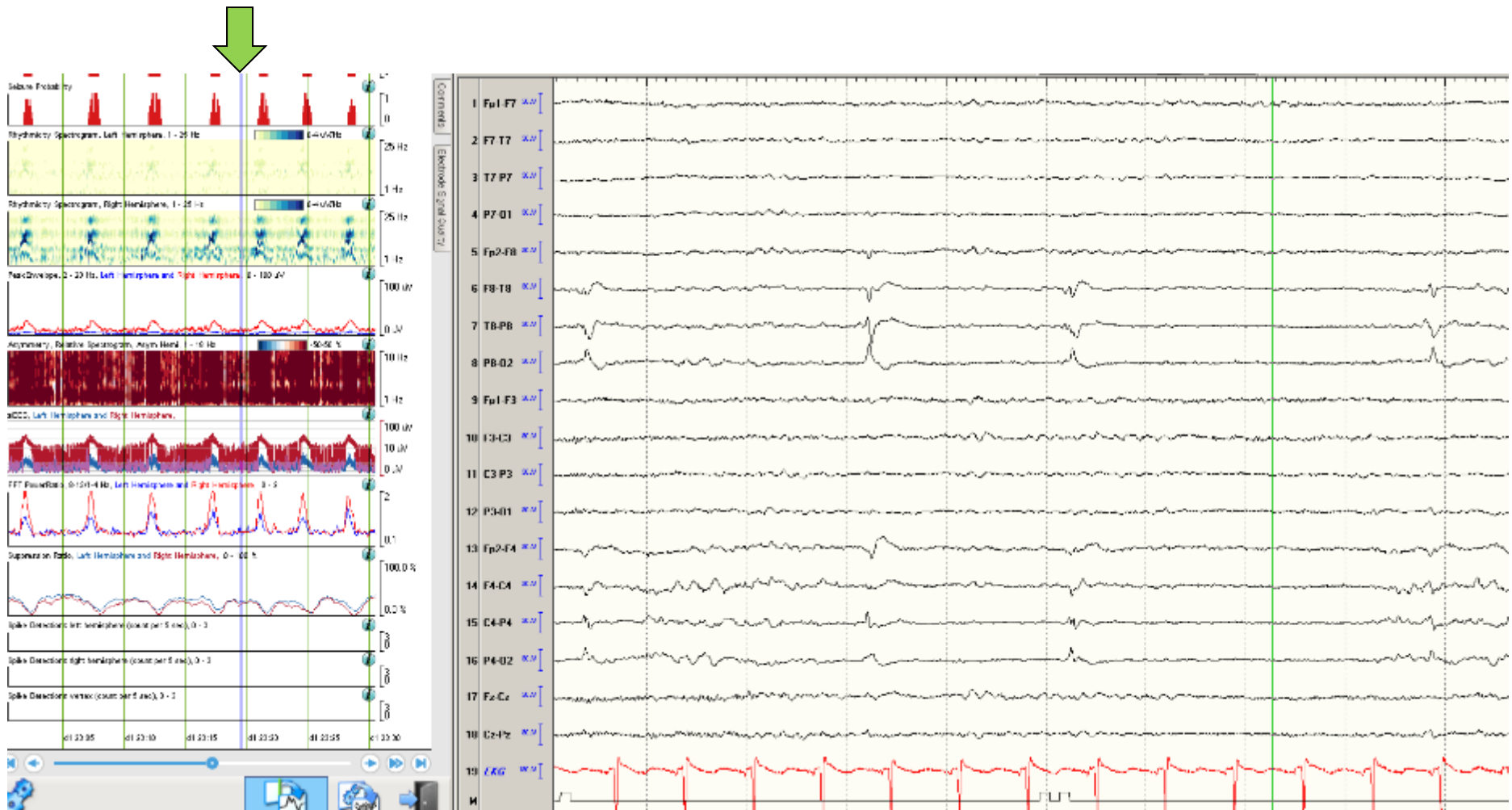
cEEG Showed a mix of bursts of spikes, periodic pattern

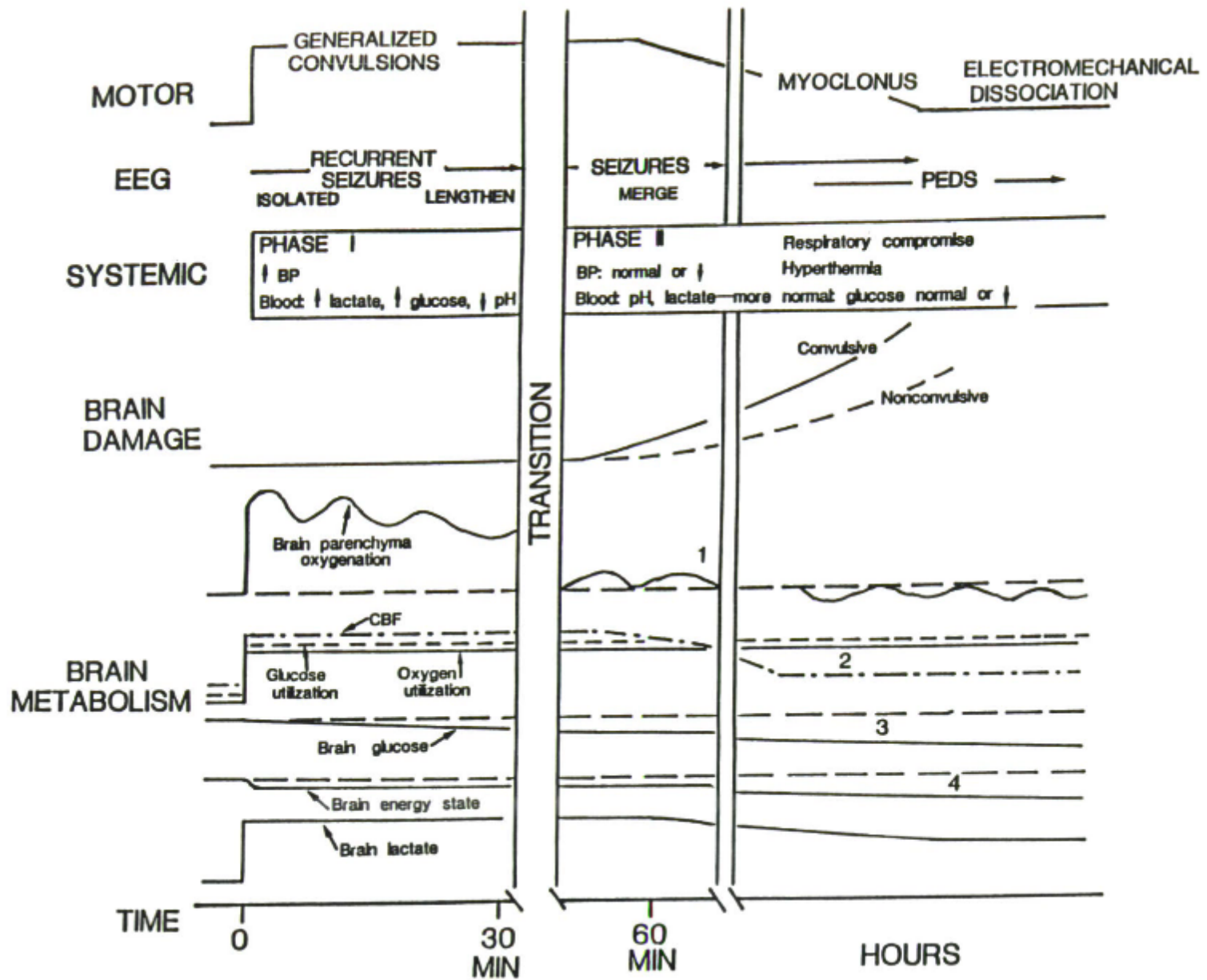


cEEG showed 14 distinct evolving EEG seizures per hour



Periodic epileptiform discharges were intermixed with isolated cEEG seizures.





Introduction

- Status Epilepticus is a medical emergency
- Prognosis is dependent on the **underlying etiology** and the amount of **time spent in status**.
- Making the diagnosis is critical and is not always straight forward, especially in the ICU setting.
- Treatment should be aggressive and appropriate to the type of status encountered, and the comorbid conditions present.

Definition of Status Epilepticus

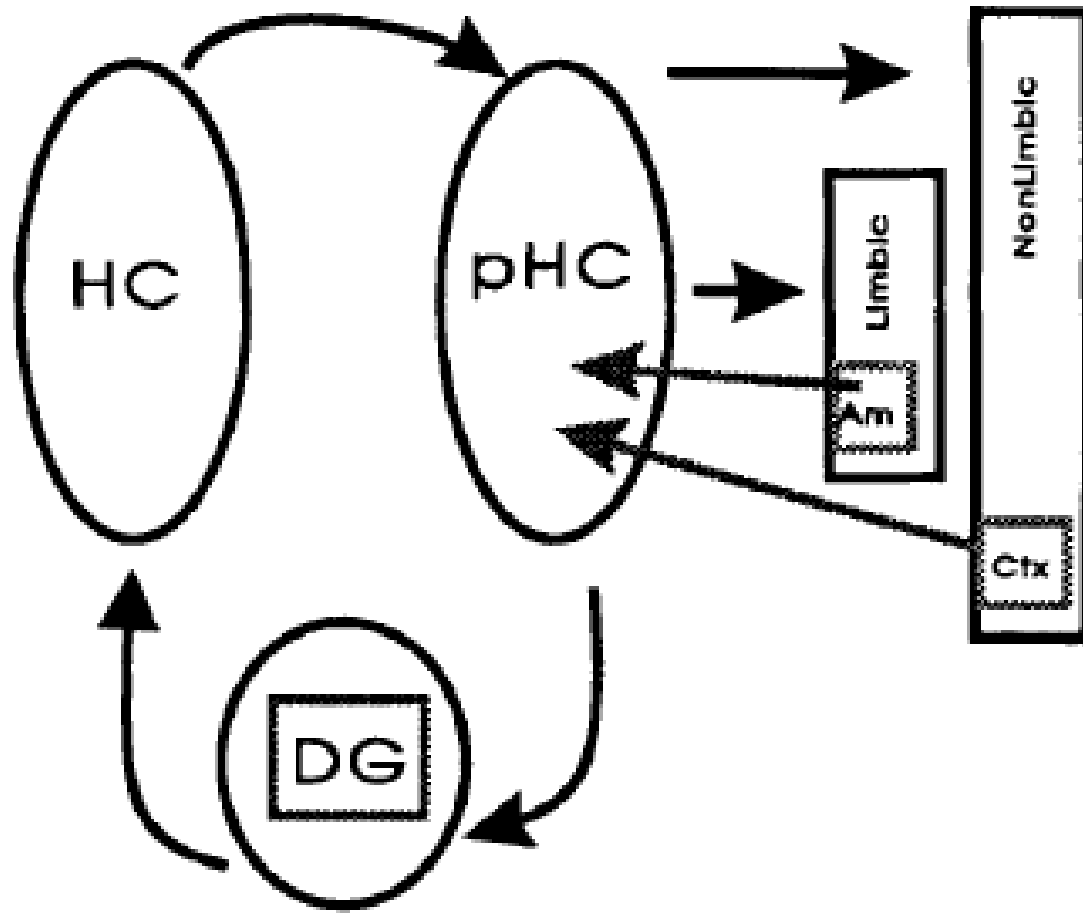
- 30 minutes of continuous seizure activity or multiple seizures without return to neurologic baseline for greater than 30 mins.
- Based on animal studies that show irreversible neuronal damage after 30 minutes of continuous seizure activity.
- This is a retrospective definition useful in defining status for studies. This should not be applied clinically.
- Working definition of Status is seizure activity that lasts **greater than 5 minutes**.

What is Refractory Status Epilepticus?

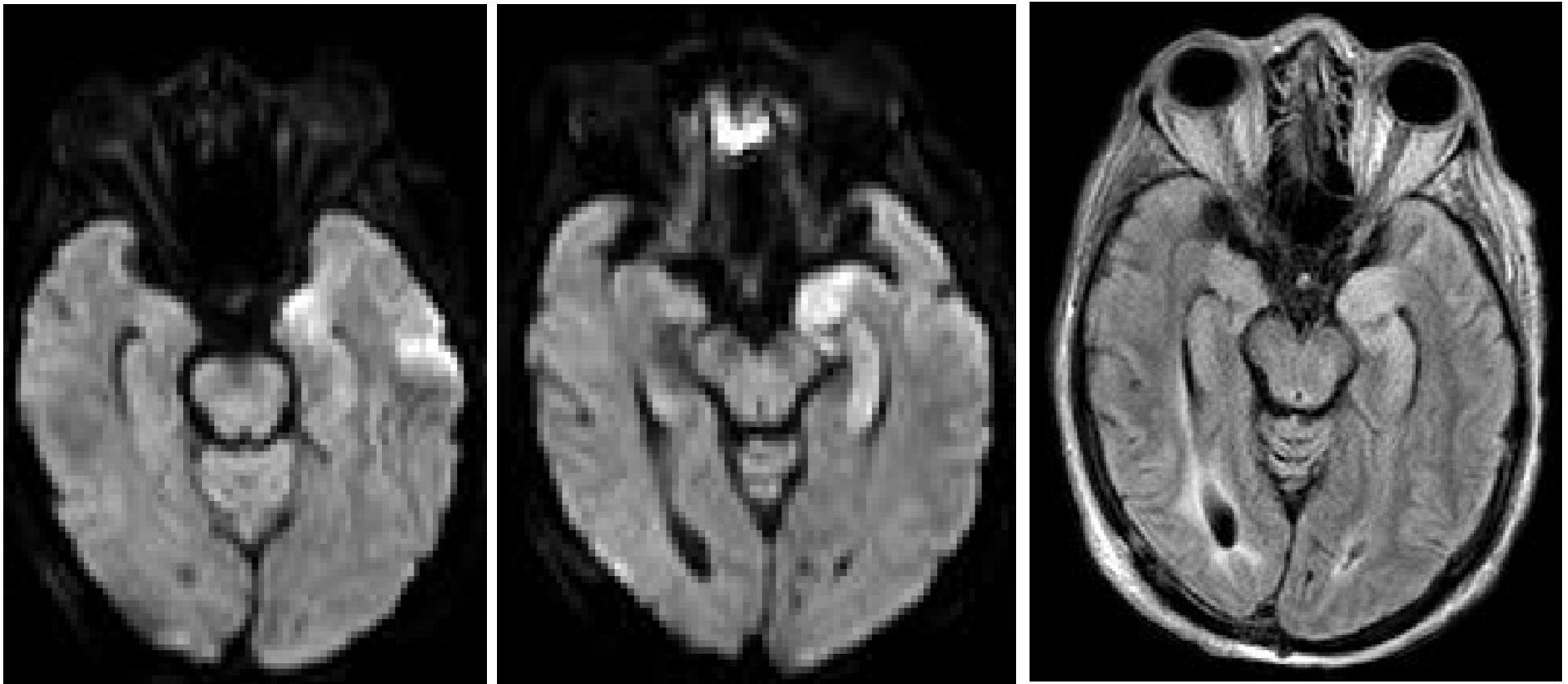
- Failure of 1st and 2nd line therapy is generally accepted

Pathophysiology

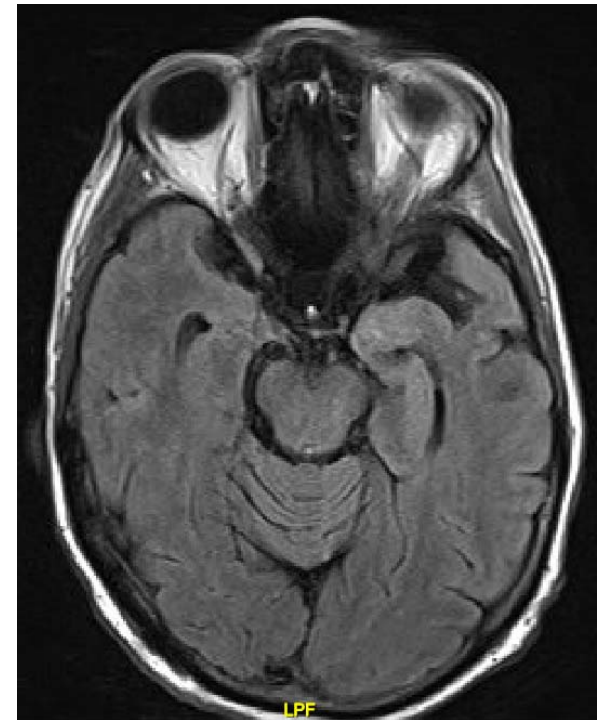
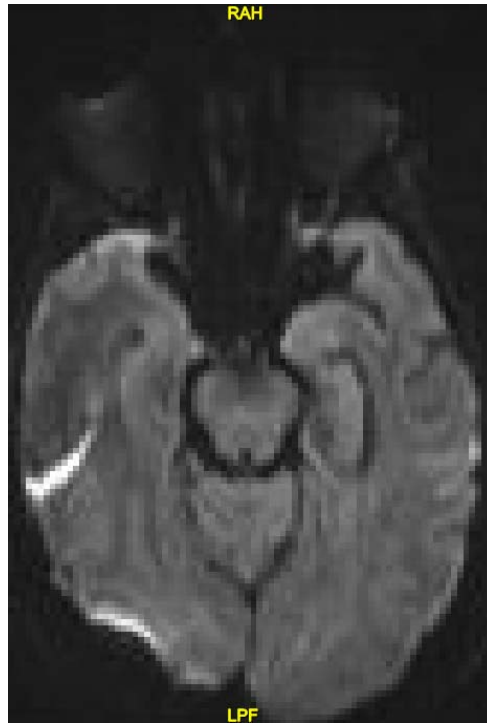
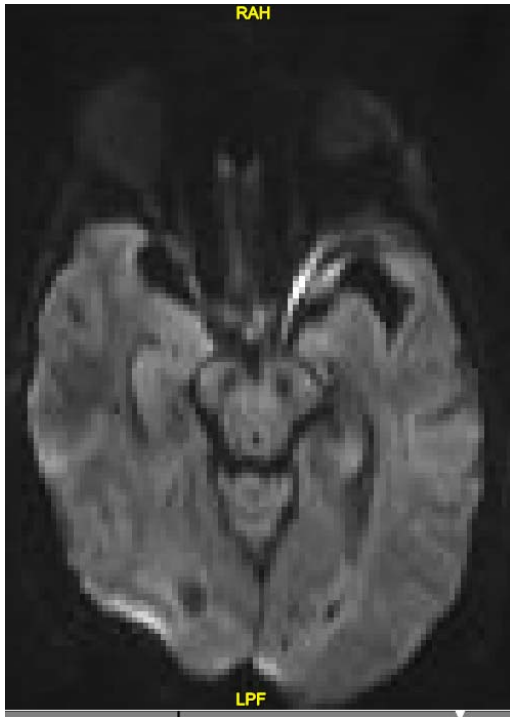
- Status epilepticus results from persistence of abnormal excitation or ineffective recruitment of inhibition.
- Induction of a reverberating seizure activity between the hippocampus and parahippocampal structures.
 - Loss of GABA mediated inhibitory synaptic transmission
 - Glutaminergic excitatory synaptic transmission is important for sustaining SE



Status Epilepticus April 13, 2013



Seizure free May 9, 2013

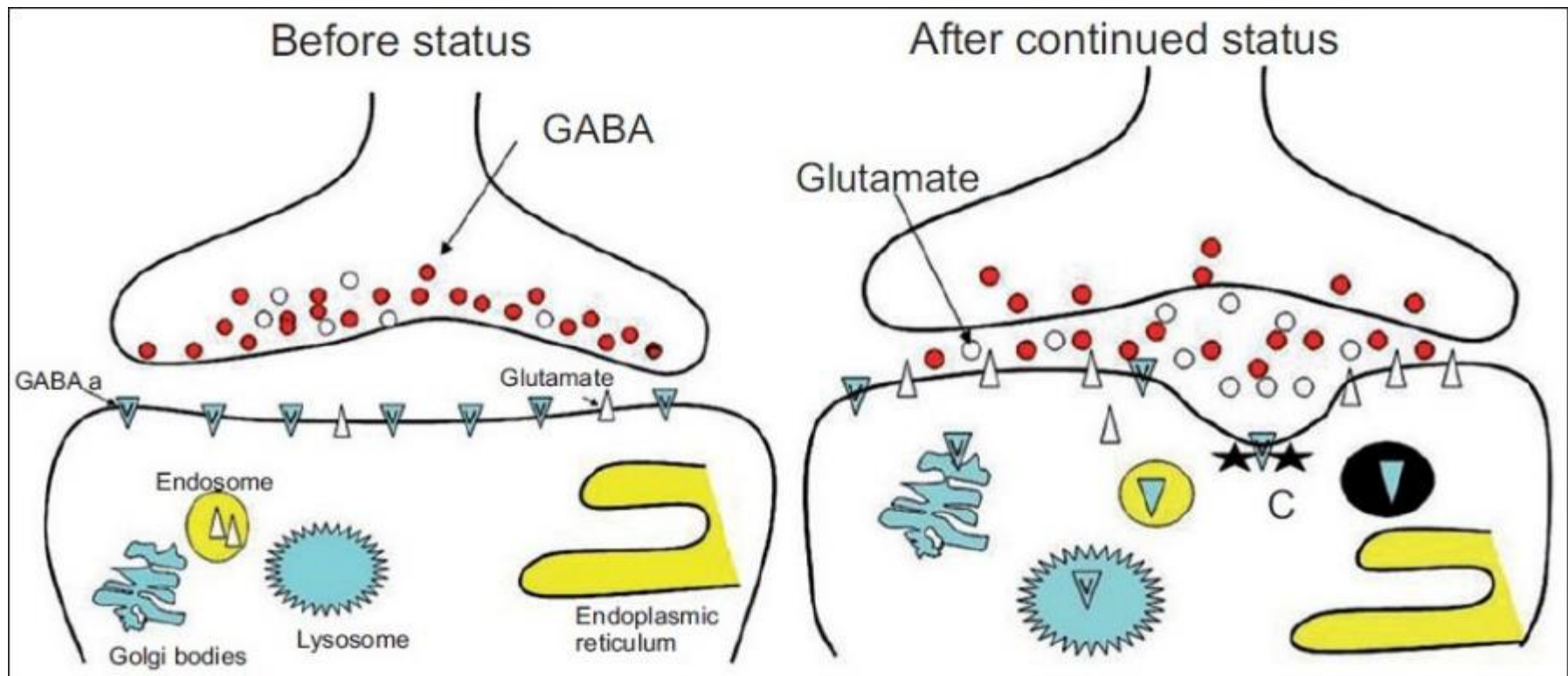


Pathophysiology

- First few seconds: Protein Phosphorylation, Opening and closure of **ion channels**, release of **neurotransmitters** and modulators
- Seconds to minutes: **Receptor trafficking** with movement of existing receptors from the synaptic membranes to endosomes or mobilization from storage sites to the synaptic membrane
 - GABA A is endocytosed out of synaptic regions
 - Glutamate receptors are moved into synaptic regions
- Minutes to hours: Plastic changes in neuropeptide modulators that are **maladaptive** resulting in a state of **raised excitability**.

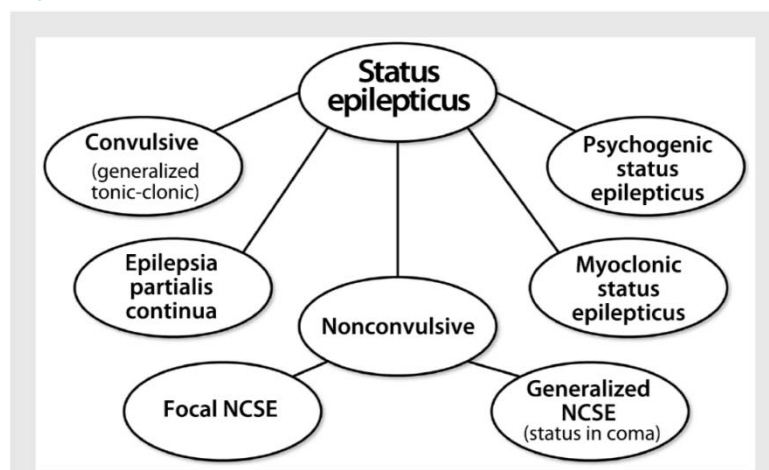
Why Does Status Become Refractory?

- Length of status
- Etiology



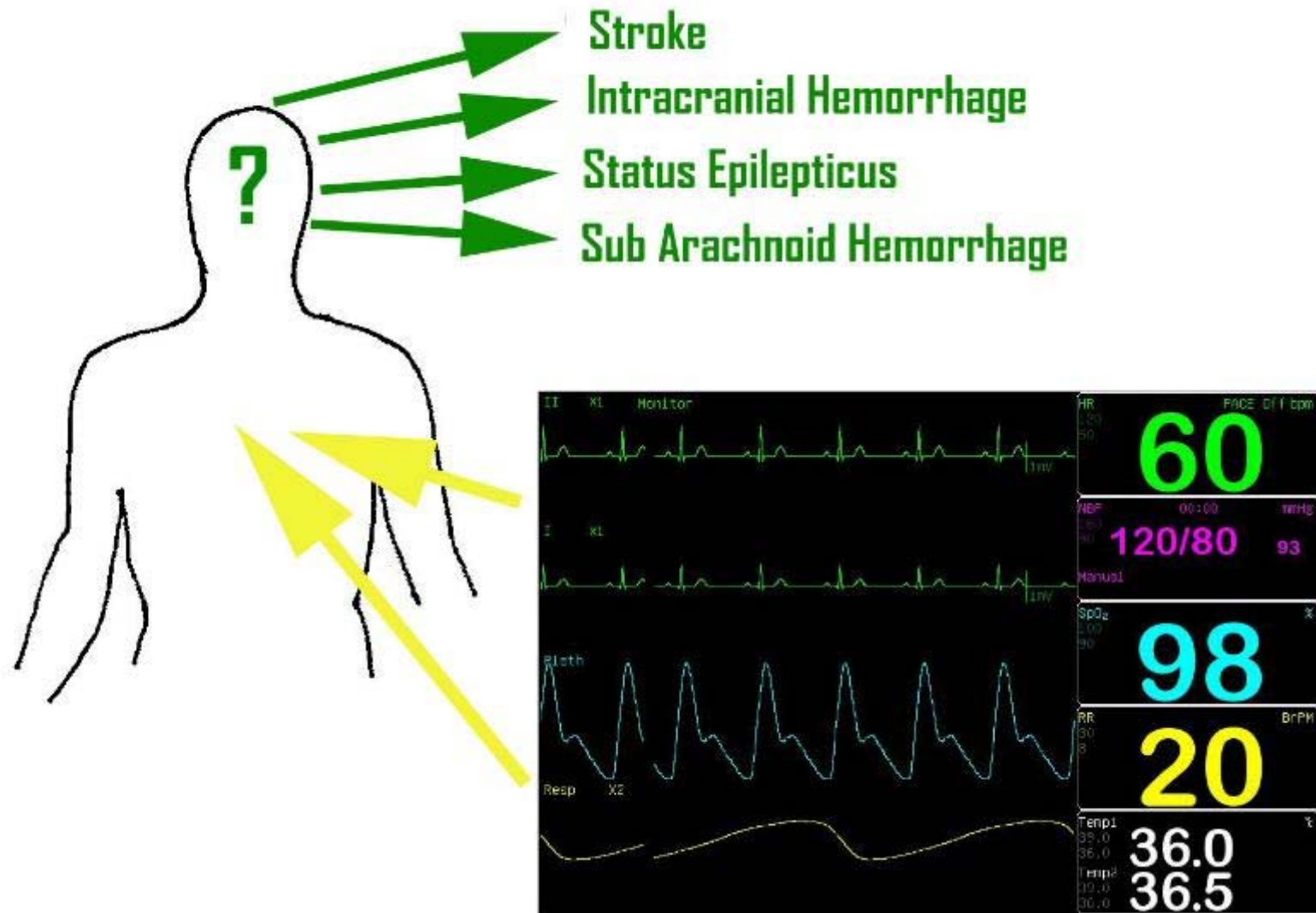
Nair PP, Kalita J, Misra UK. Status epilepticus: Why, what, and how. J Postgrad Med 2011;57:242-52

Types of Status Epilepticus

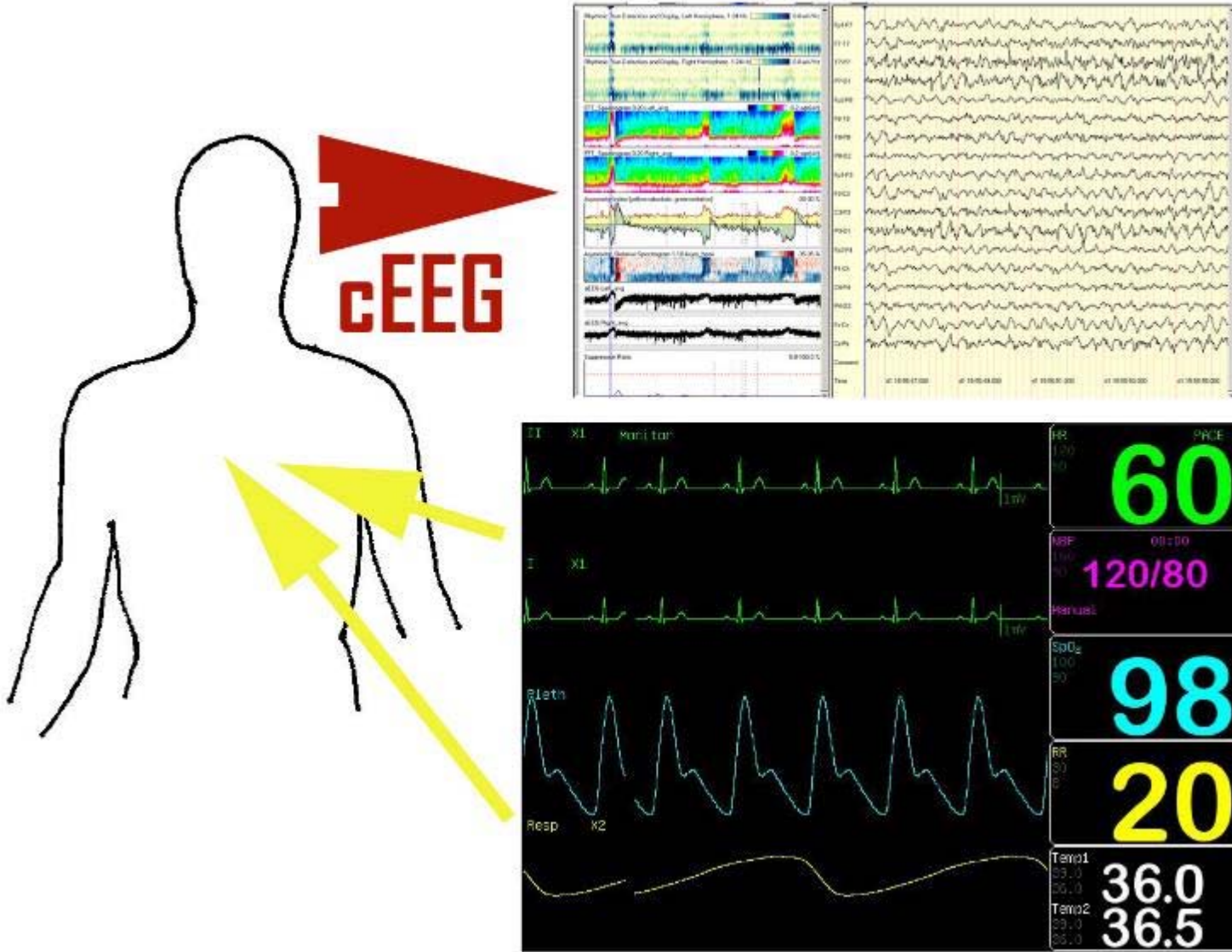


- **Generalized Convulsive Status Epilepticus - GCSE.**
 - Often easy to recognize (Even for non-specialists).
 - Standard protocols exist, initial treatment is straight forward.
- **Non Convulsive Status Epilepticus - NCSE.**
 - May present with subtle motor features as an extension of GCSE
 - Complex partial SE – with altered awareness (Focal status, ie. Right temporal, left parietal, etc)
 - Focal Motor SE (Epilepsia partialis continua) ie. left PLEDs and right facial twitching.
 - Myoclonic SE (Seen after cardiac arrest)

Neuro Intensivist are specialist in neurologic diseases and critical care.



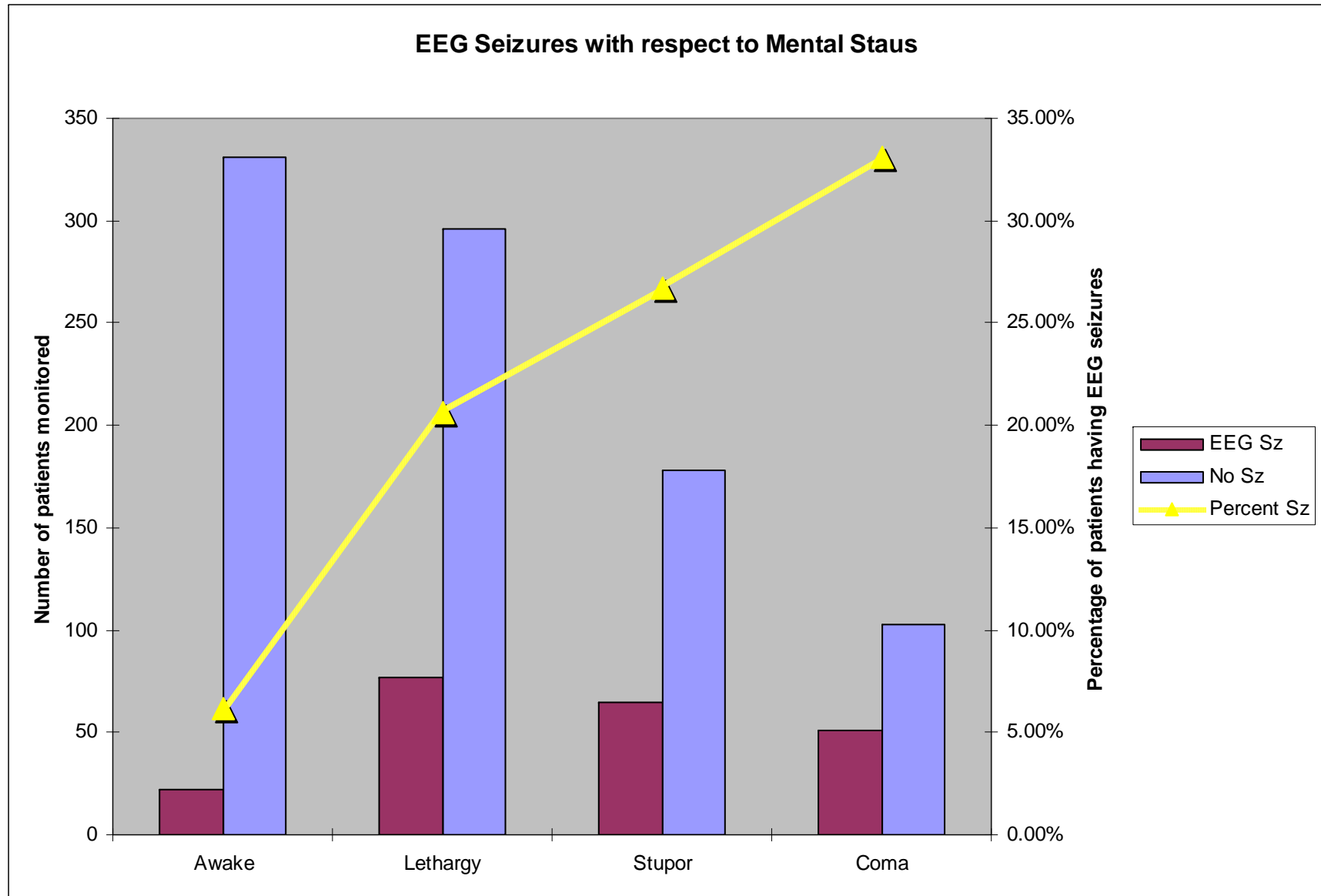
cEEG provides a method to monitor cerebral function

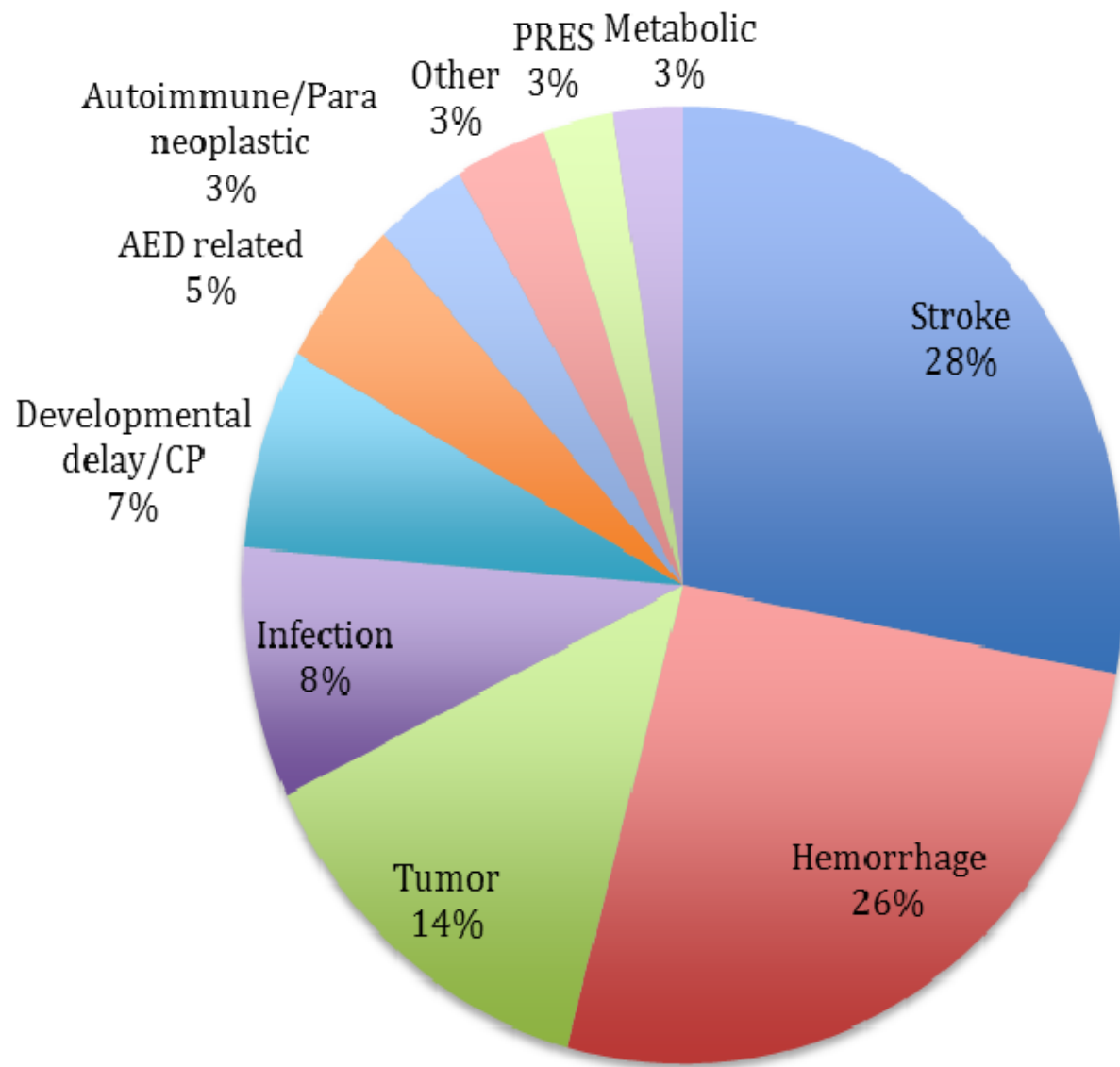


Demographics of the CCF ICU-EEG Sample

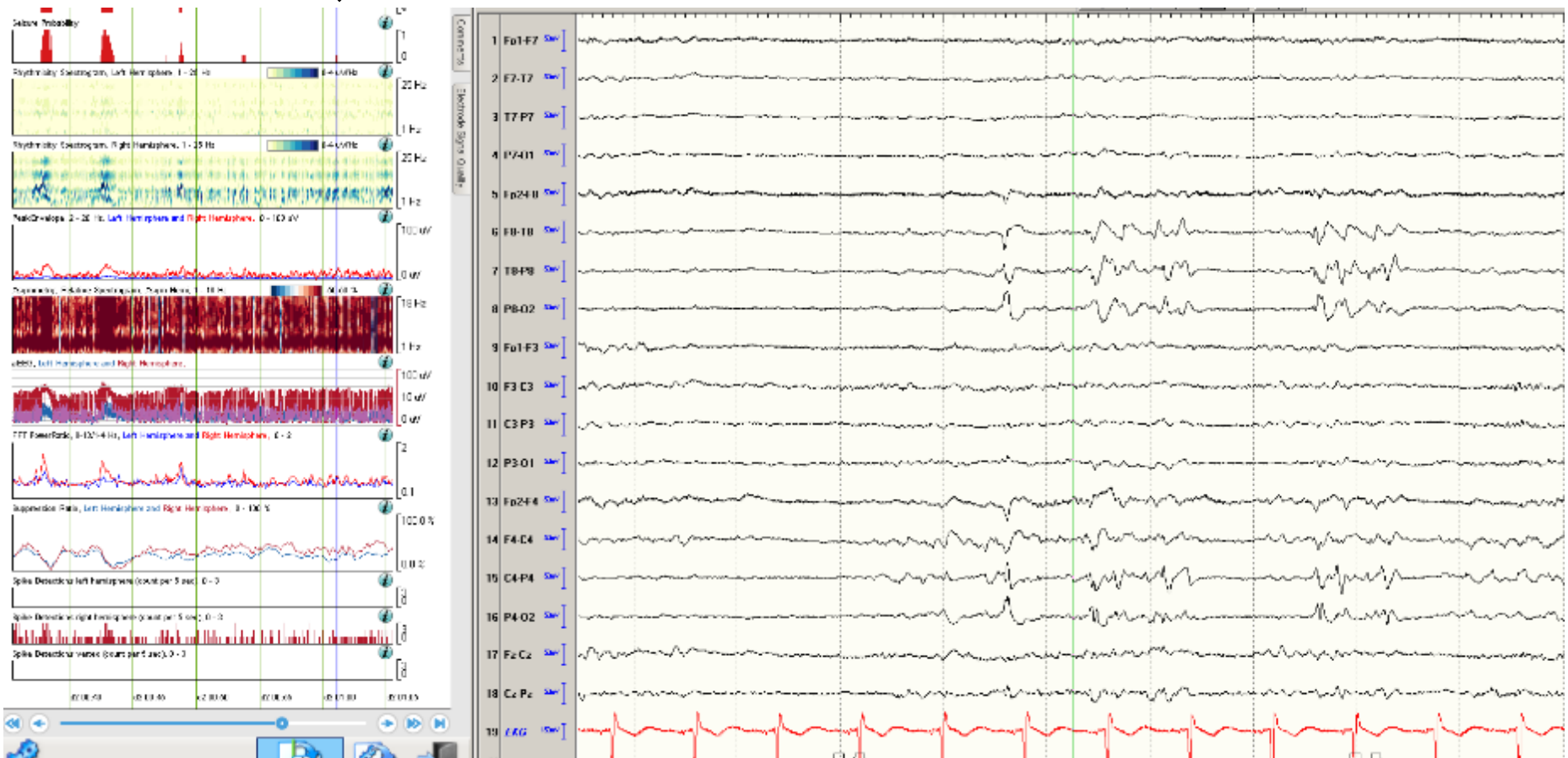
January 2009 – December 2010	EEG Sz/Status	No Sz
Overall (N = 1123)	215 (19.1%) 92% NCS	908
Mean Age	58.5	57.1
Age Range	18.6 – 93.8	18.2 – 95.8
Females	107	458
Males	108	450

Coma is Associated with EEG Seizures in One Third of Patients



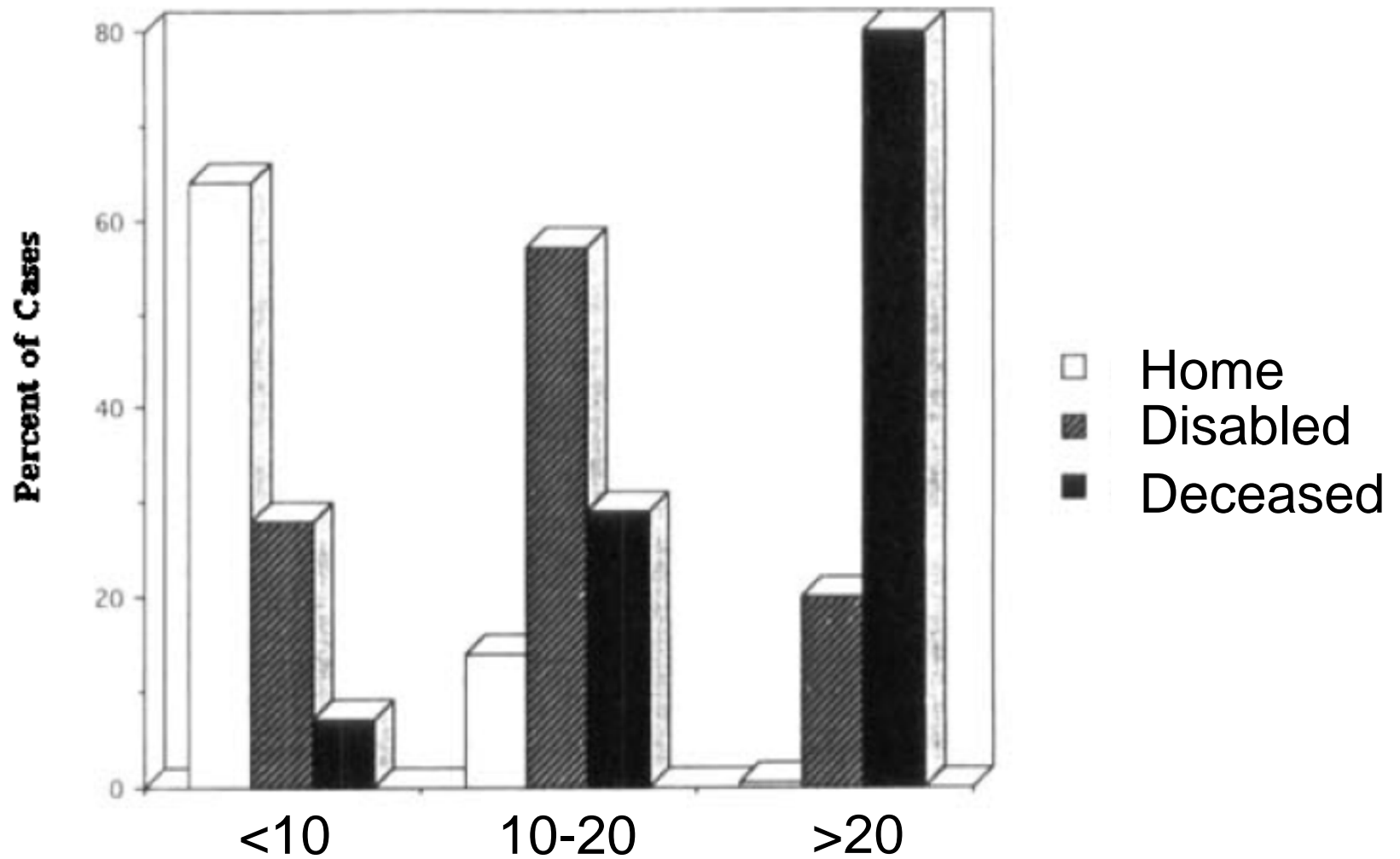


Back to our patient: Seizures stop at 6 hours after Lorazepam, Levetiracetam, Lacosamide, PHT and a Midazolam gtt.



How Long Can We Let Patients Have Seizures?

(Young et al. 1996)



Response to Treatment Depends on the Stage of SE.

Premonitory Stage

Early SE (0-30 mins)

Established SE (30-60 mins)

Refractory SE (60 + mins)

Our patient had 16+ hours of status epilepticus prior to treatment.

Physiological Consequences of Status Epilepticus

- **Hyperthermia**
 - Temp as high as 42 have been recorded after 9h of status
- **Catecholamine Release**
 - May be associated with cardiac arrhythmias, ischemic changes and elevations in glucose
- **Acidosis**
 - In one study 84% were acidotic and 32% had a pH less than 7
 - Does not seem to contribute to brain damage, may be protective against excitotoxic damage.
- **Cell Death**
 - Release of pre-synaptic glutamate results in activation of post-synaptic NMDA receptors and increase in calcium and activation of proteases, neuronal nitric oxide synthase and caspases.

Approach to Treatment

- **Termination of Status Epilepticus**

- Diagnosis is Key (GCSE, Non-Epileptic, Anoxic Injury, etc)
- Protocols for Initial Management, but do not include newer drugs.

- **Management of Underlying Etiology**

- Rapidly expanding GBM is different than non-compliance, etc

- **Treatment of Seizure Related Complications**

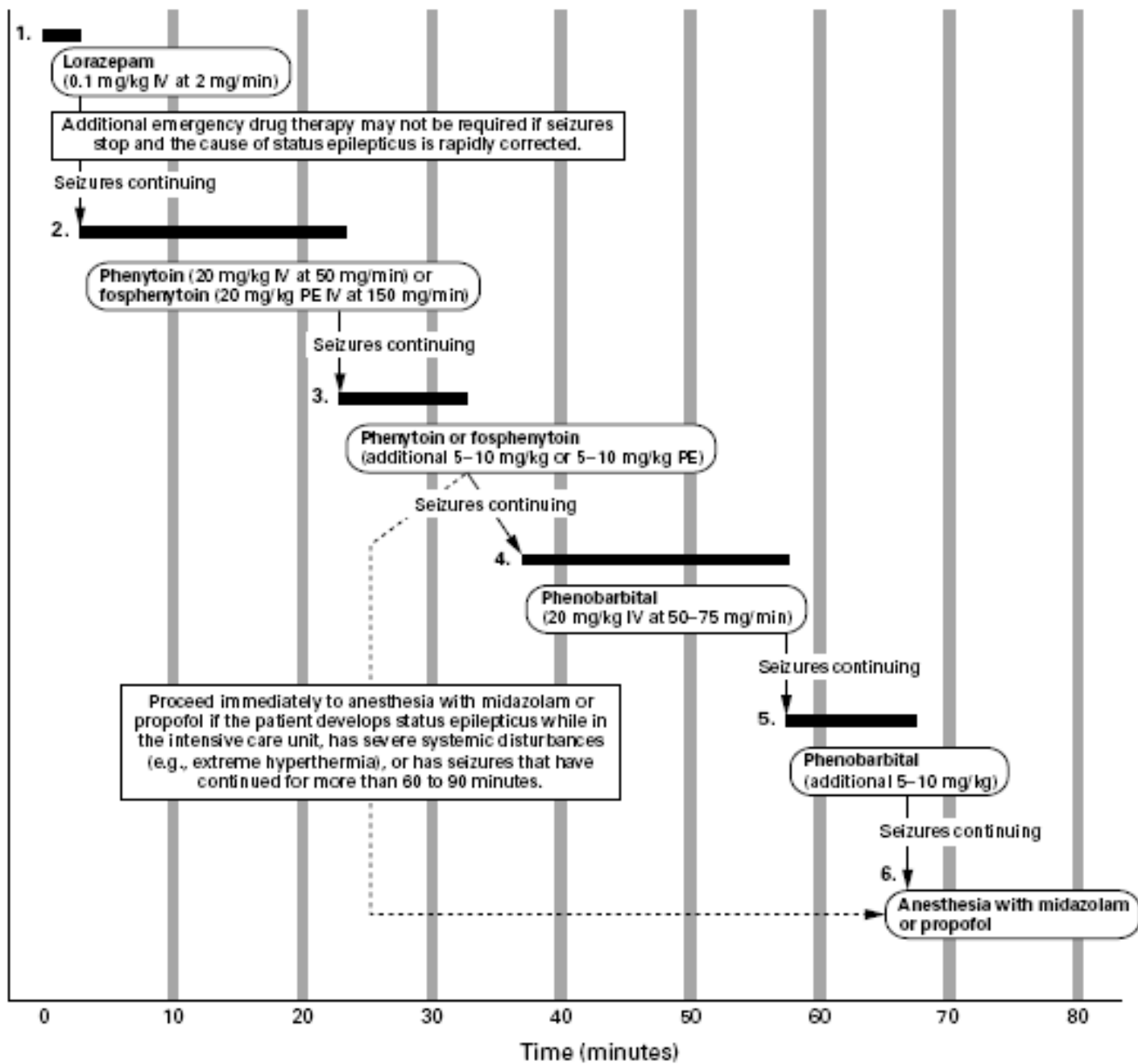
- Rhabdomyolysis, ICU neuropathy, DVTs

- **Preventing Seizure Recurrence**

- How many medications are needed? Duration of Therapy?

Initial Management

- **VA cooperative study (1988)**
 - Lorezapam 0.1 mg/kg is the established initial treatment
 - Status was controlled in 64.9% of cases with first treatment
 - Was compared to Diazepam + Phenytoin (55.8%), Phenobarbital (58.2%), and phenytoin (43.6%).



Currently Available IV Anti-Epileptic Medications

- Lorazepam/Diazepam/Midazolam (RAMPART trial, VA)
- Dilantin/ Fosphenytoin (ESET trial, VA)
- Phenobarbital (VA)
- Valproate (ESET trial)
- Levetiracetam (ESET trial)
- Lacosamide (TRENDS)
- Briviracetam
- Allopregnanolone (SAGE-547 trial)

RAMPART Trial

- Pre-hospital treatment trial
- Randomized 4mg IM midazolam in an Autoinjector against IV lorazepam (Standard of care).
- IM Midazolam had 76% efficacy and was thought to be more efficacious because it was delivered faster.

Guidelines for the Evaluation and Management of Status Epilepticus

Gretchen M. Brophy · Rodney Bell · Jan Claassen · Brian Alldredge ·
Thomas P. Bleck · Tracy Glauser · Suzette M. LaRoche · James J. Riviello Jr. ·
Lori Shutter · Michael R. Sperling · David M. Treiman · Paul M. Vespa ·
Neurocritical Care Society Status Epilepticus Guideline Writing Committee

Table 1 Evidence rating system based on American Heart Association/American College of Cardiology guidelines [4]

Class category	Level of evidence
I Intervention is useful and effective. Treatment benefits clearly exceed risks	A Adequate evidence is available from multiple, large, randomized clinical trials or meta-analyses
IIa Evidence/expert opinion suggest intervention is useful/effective. Treatment benefits exceed risk	B Limited evidence is available from less rigorous data, including fewer, smaller randomized trials, nonrandomized studies, and observational analyses
IIb Strength of evidence/expert opinion about intervention usefulness/effectiveness is less well established. More data are needed; however, using this treatment when warranted is not unreasonable	C Evidence relies on expert/consensus opinion, case reports, or standard of care
III Intervention is not useful or effective and may be harmful. Benefit does not exceed risk	

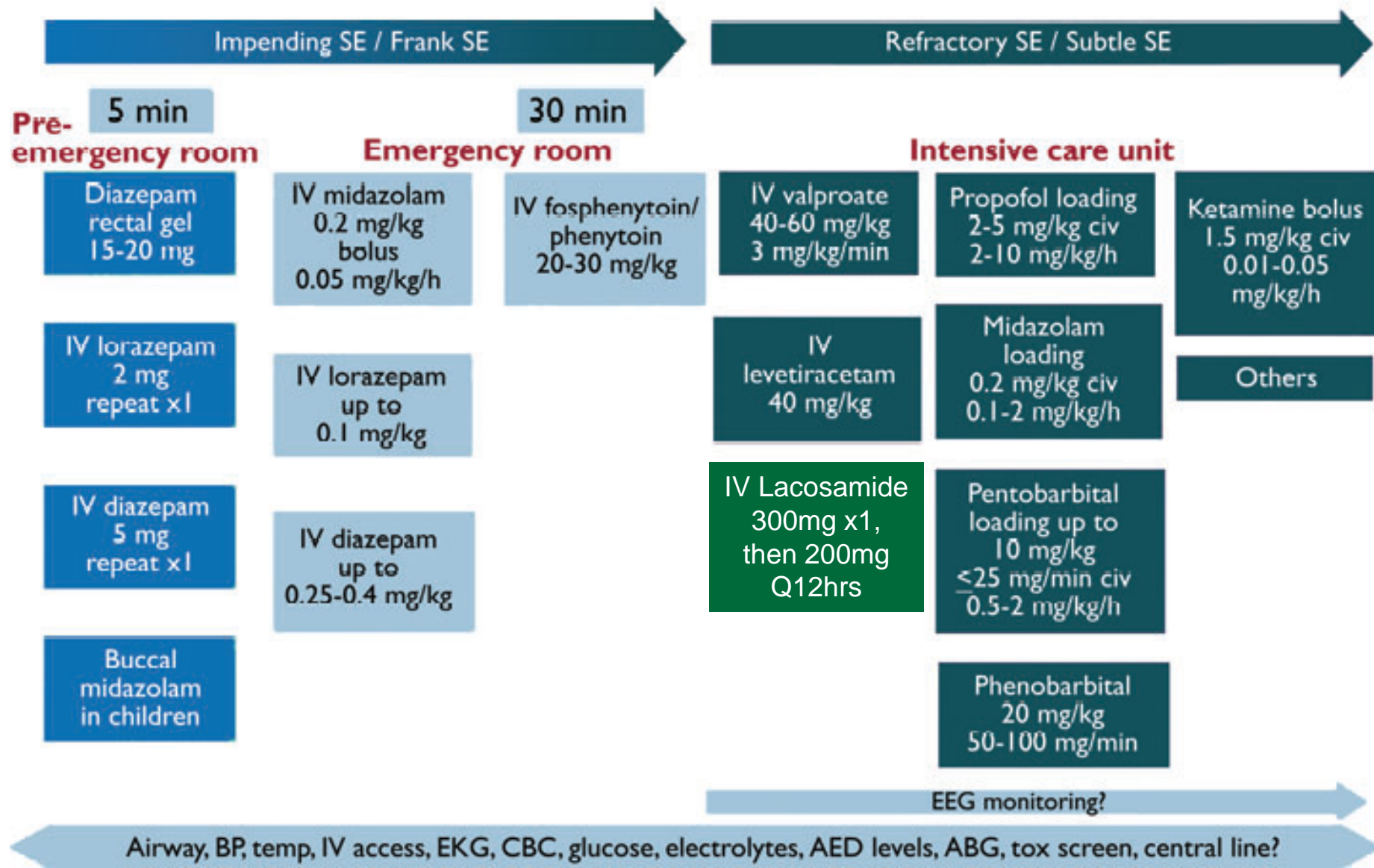
Table 6 Treatment recommendations for SE

Treatment	Class/level of evidence
Emergent treatment	
Lorazepam	Class I, level A
Midazolam	Class I, level A
Diazepam	Class IIa, level A
Phenytoin/fosphenytoin	Class IIb, level A
Phenobarbital	Class IIb, level A
Valproate sodium	Class IIb, level A
Levetiracetam	Class IIb, level C

Established Status Epilepticus Treatment Trial (ESETT)

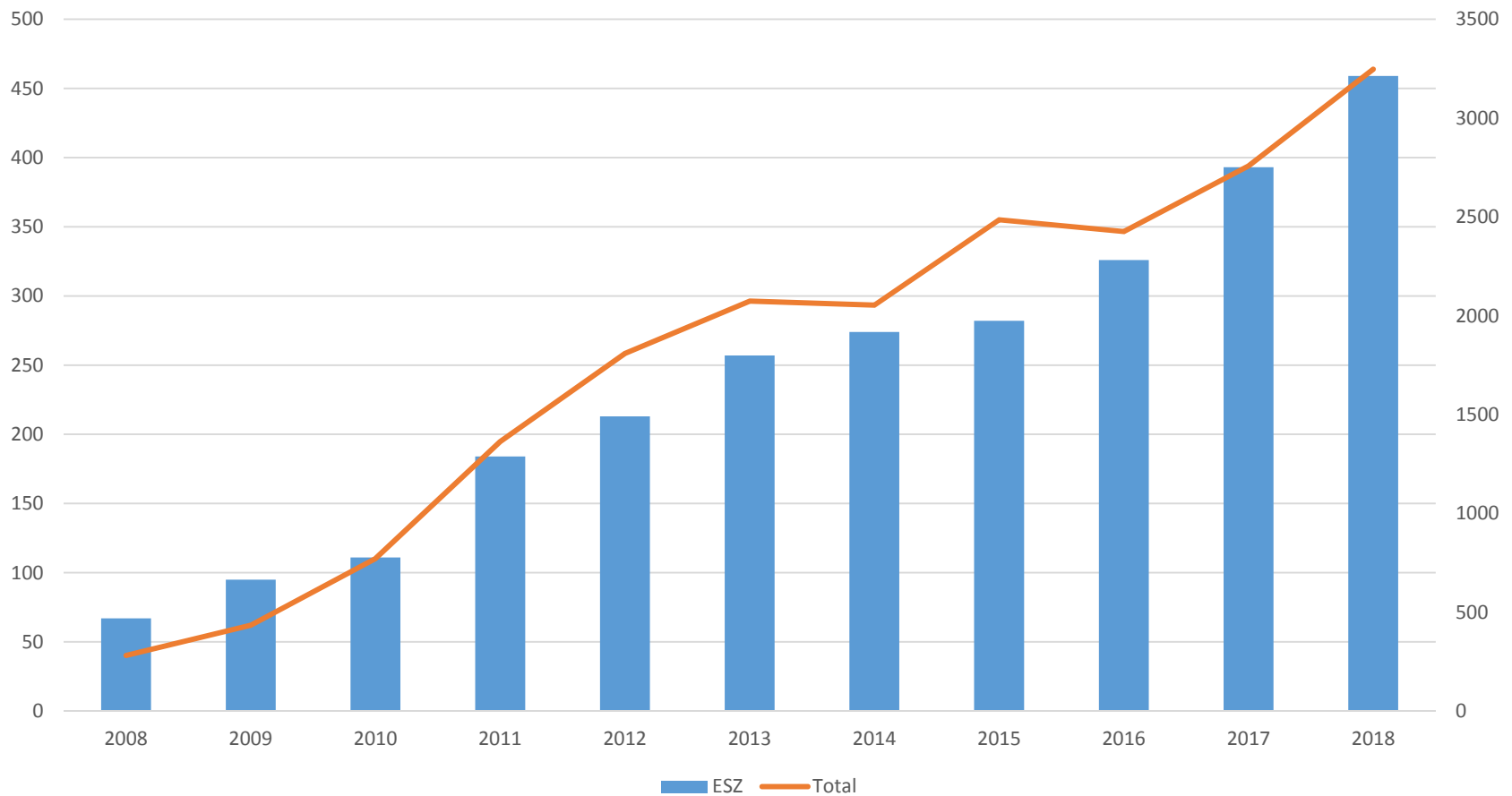
- Patients had benzodiazepine resistant status epilepticus
- large, high-quality, randomized controlled trial (RCT)
- levetiracetam at a dose of 60 mg per kilogram (maximum, 4500 mg),
- fosphenytoin at a dose of 20 mgPE per kilogram (maximum, 1500 mgPE)
- valproate at a dose of 40 mg per kilogram (maximum, 3000 mg).
- These three drugs showed similar effectiveness and incidence of adverse events

Management of GCSE in adults



Evolution of cEEG seizure detection at the Cleveland Clinic

10 years of cEEG monitoring
Consistent increase in seizures detected with increased monitoring



Questions? Discussion...

