

# *Seizures in the Neuro-ICU*

*Lori A. Shutter, MD*

***lori.shutter@uc.edu***

*Director, NSICU/Neurocritical Program*

*Assoc. Professor, Clinical Neurosurgery & Neurology*

*University of Cincinnati Medical Center*

***<http://www.ucneurocriticalcare.com/physicians>***

# Disclosures / Objectives

- Disclosures: Grants / Research
  - NIH, DoD, UCB Pharma
- Objectives
  - Review definitions & incidence of status epilepticus
  - Discuss treatment options for status epilepticus

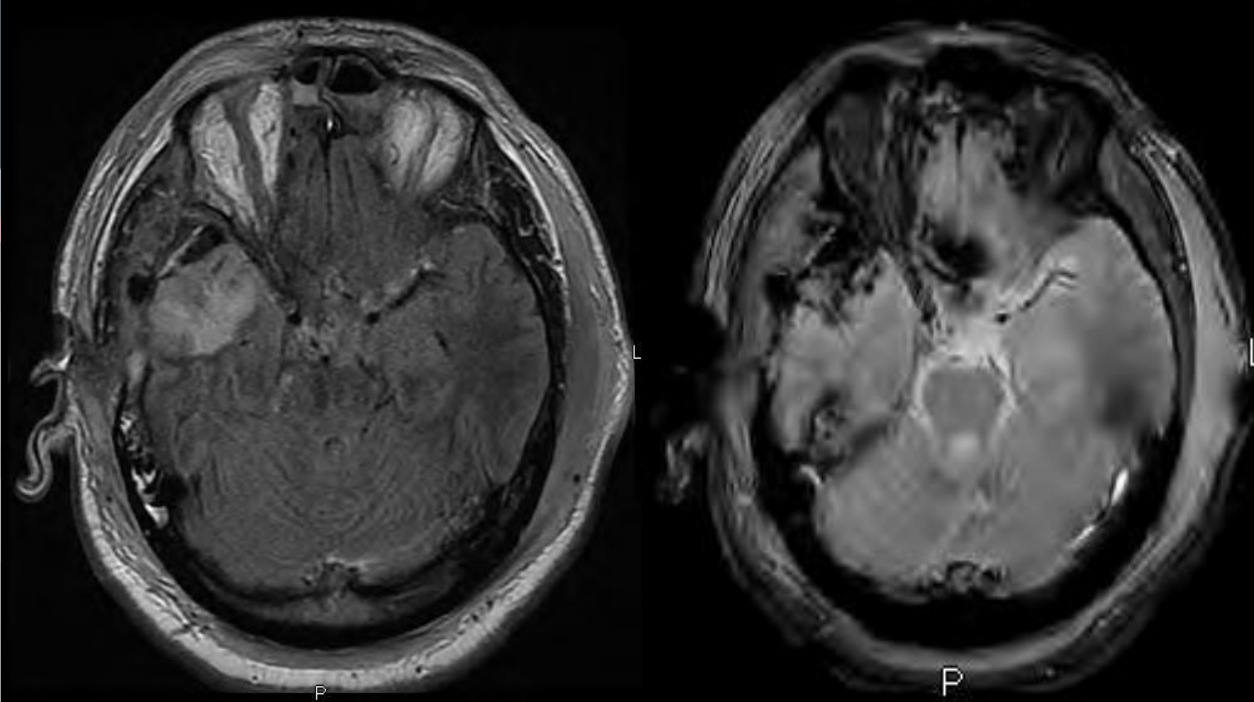
# Case Presentation

61 yo M presents after a fall with a GCS of 14



Taken to OR for decompression





## MRI

Pt localizing  
3d post injury  
AEDs stopped



## CT

4d post injury  
Pt now only withdrawing  
intermittently

# EEG @ 19:30



# EEG @ 21:00:01



# EEG @ 21:00:50

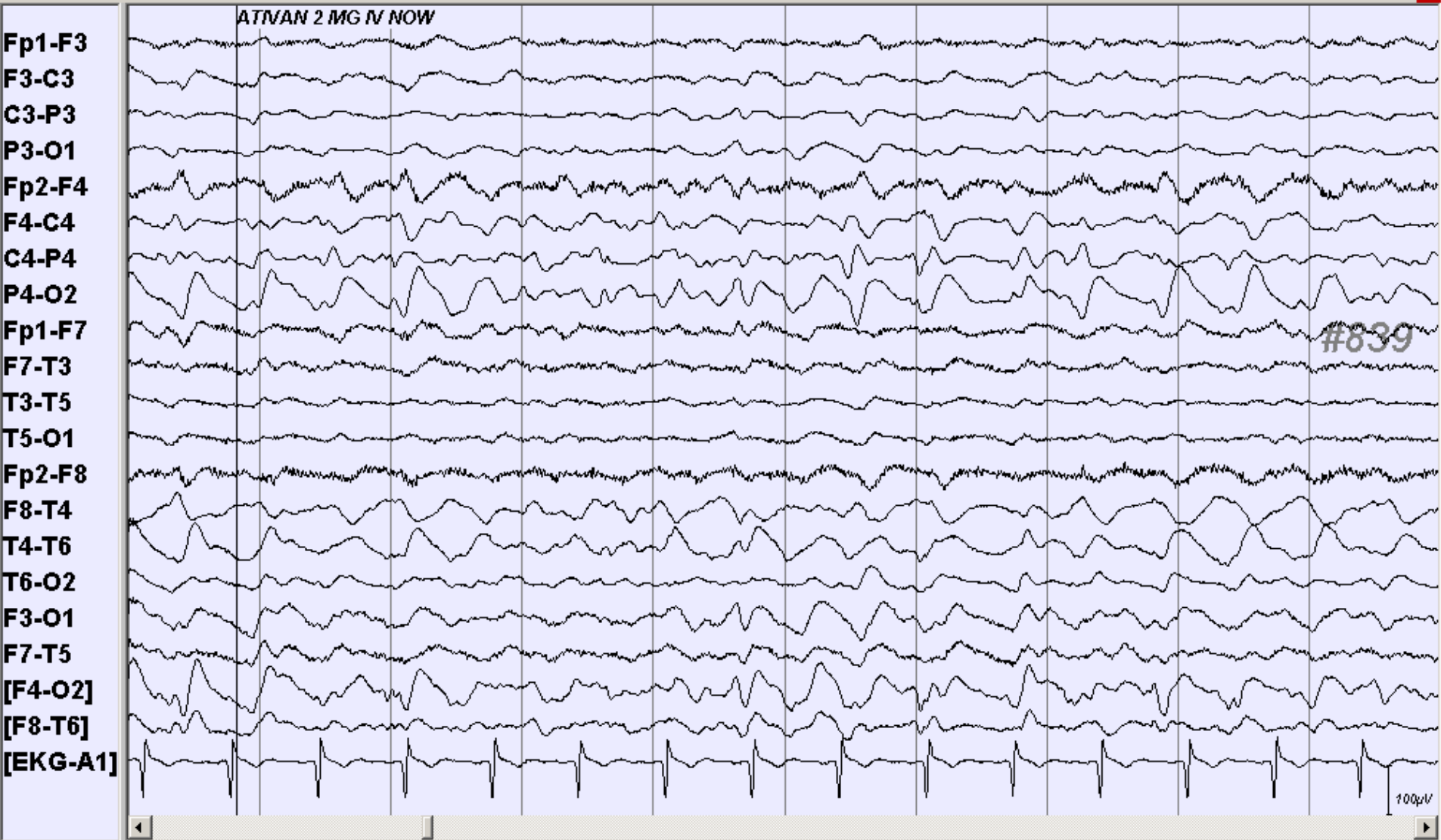


# Questions

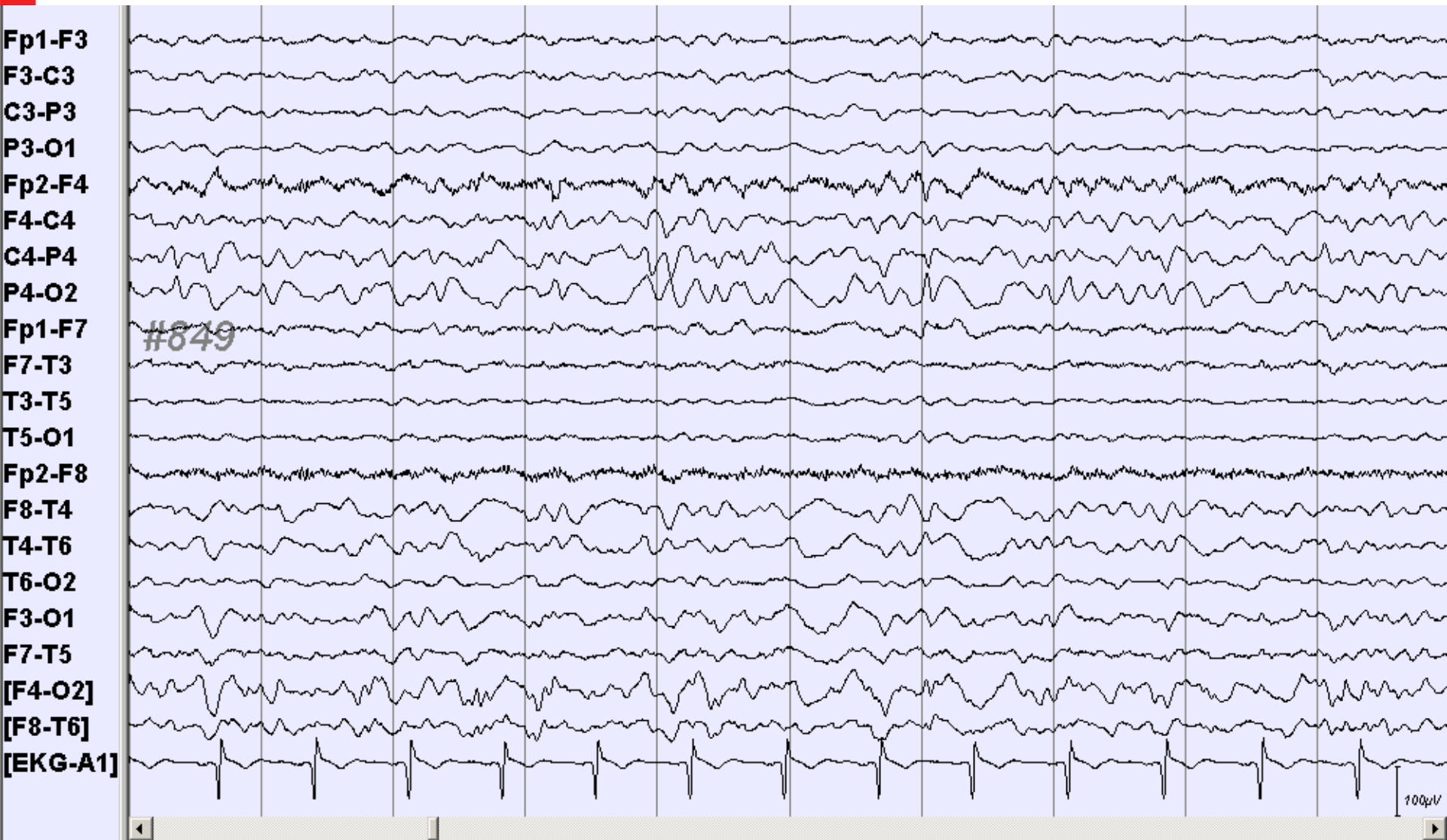
- **Are these seizures?**
- **Should this be treated?**

# EEG @ 21:45:15

Given ativan, then loaded with LEV 1000 mg bid



# EEG @ 21:47:04



# Status Epilepticus

- Definition:
  - Traditional: Any type of seizure lasting > 30 minutes, or 2 or more sequential seizures without full recovery of consciousness between them (*JAMA 1993*)
  - Modern: any seizure lasting > 10 minutes\*\*
  - Practical: any patient who is still seizing
  - Motor / Convulsive OR Electrographic / Non-convulsive
  - Refractory: not responsive to standard 1<sup>st</sup> / 2<sup>nd</sup> line therapies
- Neurological emergency
  - Prolonged seizures resultant in neuronal injury

# Status Epilepticus: Etiology

- Prior history of epilepsy
  - AED modifications or non-compliance
  - Systemic infections
  - Physical or emotional stressors (sleep deprivation)
- Acute CNS injury or insult
  - Infectious: meningitis / encephalitis / abscess
  - Trauma
  - Anoxia
  - Metabolic encephalopathies
  - Drug intoxication / withdrawal
  - Strokes, especially hemorrhagic events
  - Mass lesions / Tumors
- Unprovoked / Idiopathic

# Prognosis: CSE

- Mortality: 9-21%<sup>1-4</sup>
- New disabling neurological deficits: ~10%<sup>5</sup>
- Some functional deterioration in 23-26%<sup>1,2,4</sup>
- Predictors of worse outcome
  - Age (higher mortality in elder pts)
  - Etiology (acute symptomatic worst)
  - Long SE duration, continuous szs
  - Nonconvulsive szs; +/-periodic discharges

*1. Alldredge et al, NEJM 2001*

*2. Claassen et al, Neurology 2002*

*3. Rosetti et al, JNNP 2006*

*4. Novy et al, Epilepsia 2010*

*5. Hirsch and Claassen, Current Neurology and Neuroscience Reports, 2002.*

# Prognosis: NCSE / RSE

## NCSE

- Mortality: 18-52%<sup>1-3</sup>

## RSE

- Mortality: 23-61%<sup>4-6</sup>

1. *Young et al, Neurology 1996*
2. *Litt et al, Epil 1998*
3. *Shneker et al, 2003*
4. *Claassen et al, Neurology 2002*
5. *Rosetti et al, JNNP 2006*
6. *Novy et al, Epilepsia 2010*

# Refractory SE: Prognosis

- Some studies have reported 50% mortality <sup>1</sup>
- Poor prognosticators: same as for SE
- For RSE, most important predictor of outcome is duration of SE.
  - Mortality = 32% (SE > 60 mins) vs. 2.7% (SE 30-59 mins)
- Conflicting evidence for prognosis of NCSE.
  - Mortality rates range from 18-52% (depending on duration, etiology, delayed dx) <sup>2</sup>

1. *Hirsch and Claassen, Current Neurology and Neuroscience Reports, 2002.*

2. *Abou Khaled et al. Crit Care Clin, 2006.*

# Basis for cEEG

- Linked to cerebral metabolism
- Sensitive to cerebral ischemia & hypoxia
  - Window of reversibility for secondary injury
- Can detect changes when exam may not
- Incidence of seizures in neurological patient
- Dynamic monitoring
- Localization
- Diagnosis of abnormal movements
  - Posturing, spasms, tremors, myoclonus, etc

# Seizure Incidence in the ICU

- cEEG in 124 ICU patients<sup>1</sup>
  - Stroke, ICH, seizures, metabolic coma, tumors, trauma
  - Overall seizure rate = 35%.
  - > 75% of these were non-convulsive events or status
- EEG for AMS or SE w/o further clinical sz (n=198)<sup>2</sup>
  - EEG with definite or probable SE in 74 (37%)
  - Altered LOC was only clinical sign in 23 cases, subtle motor activity present in 36 others

1. Jordan K. *Neurol Clin* 1995; 13:579-626

2. Privitera M, et al. *Epilepsy Res* 1994; 18:155-166

# Seizure Incidence in the ICU

- Prospective trial of cEEG x 48 hours in 55 comatose patients
  - Excluded: cardiac arrest, brain death, recognized status epilepticus, anesthesia
  - 2 groups:
    - acute structural lesion (31)
    - metabolic abnormality (24)
- Seizures recorded in **20%** (11) of patients
  - **32%** (10/31) of patients with structural lesions. Only 2 of these had clinically recognized seizures.
  - **4%** (1/24) of patients with metabolic disorders

# Seizure Incidence in the ICU

- Retrospective review of 570 patients undergoing continuous EEG in the Neuro-ICU
- All were on prophylactic anticonvulsants
- Indication for monitoring:
  - Unexplained decrease in LOC
  - Detection of subclinical seizures
- Time to 1<sup>st</sup> seizure:
  - 88% within 24 hrs; 93% within 48 hrs
- Seizure frequency
  - Seizures occurred in 110 patients (19%)
  - 101 of these 110 patients (92%) had only NCSE

# Seizure Incidence in the ICU

Diagnosis	N	Any Sz (%)	NCS (%)	NCSE (%)
<b>Epilepsy</b>	<b>51</b>	<b>17 (33)</b>	<b>16 (31)</b>	<b>10 (20)</b>
<b>CNS Infection</b>	<b>35</b>	<b>10 (29)</b>	<b>9 (26)</b>	<b>6 (17)</b>
<b>Brain Tumor</b>	<b>43</b>	<b>10 (23)</b>	<b>10 (23)</b>	<b>5 (12)</b>
<b>SAH</b>	<b>108</b>	<b>20 (19)</b>	<b>19 (18)</b>	<b>14 (13)</b>
<b>TBI</b>	<b>51</b>	<b>9 (18)</b>	<b>9 (18)</b>	<b>4 (8)</b>
<b>↓ LOC (NOE)</b>	<b>105</b>	<b>17 (17)</b>	<b>16 (15)</b>	<b>5 (5)</b>
<b>ICH</b>	<b>45</b>	<b>6 (13)</b>	<b>6 (13)</b>	<b>4 (9)</b>
<b>CVA</b>	<b>56</b>	<b>6 (11)</b>	<b>5 (9)</b>	<b>4 (7)</b>

# Risk Factors for Seizures

1. Coma
  - 57% of comatose patients had seizures on cEEG
2. Age < 18
3. Past history of seizures
4. Convulsive seizures prior to monitoring
  - Incidence of seizure relative to risk factors
    - 2 of 4 = 40%
    - 3 of 4 = 65%
    - 4 of 4 = 88%

# Non-Convulsive Status Epilepticus

- 13 – 49% of pts will have non-convulsive seizures or SE after clinical convulsions stop
- Mortality higher in these patients independent of age or cause
- EEG is mandatory after SE if patient does not wake up quickly

# Subarachnoid Hemorrhage

- 100 stuporous or comatose SAH patients
- Only 26 placed on cEEG
- 8 of the 26 (31%) noted to have NCSE
- Diagnosed on average 18 days after SAH (range = 5 – 38d)

# Traumatic Brain Injury

- 94 patients, prospective study
- Continuous EEG
- Prophylactic AEDs
  - Mean AED level at time of seizure = 16.6 mg/dl
- Seizures in 24% (21)
  - 52% of the seizures were non-convulsive
  - 6 patients with status, all died
- 90% (19/21) had seizure within 72 hours

# Stroke

- 109 patients; ischemic stroke in 46, ICH in 63.
- cEEG, most seizures occurred in 1<sup>st</sup> 72 hours
- Seizure incidence:
  - ICH = 28% (18/63)
  - Ischemic stroke = 6% (3/46)
- Type: focal with secondary generalization
- More common in lobar hemorrhages (34%)
  - But did occur in 21% of subcortical hemorrhages
- Seizures were associated with neurological worsening, increased MLS and worse outcomes

# TUH Indications for cEEG

- Not awakening after a convulsive seizure or SE
- Transferred from another hospital for refractory SE or to rule out NCSE
- Ongoing or frequently recurring clinical events that are suspicious for seizures
- AMS without clear explanation
- Characterize spells in comatose patients that may represent seizures
  - including autonomic spells such as sudden hypertension, tachycardia, apnea, or bradycardia
- Duration
  - 24 hrs if awake; 72 hrs for all others

# Managing Status Epilepticus

- Goals of Therapy
  - Control seizures with minimal adverse effects
  - Maintain or restore normal functioning and activities
  - Assess response to AED's at steady state
  - Be aware of potential drug interactions

# Available AEDs

## Older Agents

- Carbamazepine (CBZ)
- Phenytoin (PTN)
- Phenobarbital (PB)
- Primidone (PRM)
- Valproic Acid (VPA)
- Ethosuximide (ESM)

## Newer Agents

- Felbamate (FBM)
- Gabapentin (GBP)
- Lamotrigine (LTG)
- Topiramate (TPM)
- Tiagabine (TGB)
- Oxcarbazepine (OXC)
- Levetiracetam (LEV)
- Zonisamide (ZNS)
- Pregabalin (PRG)
- Lacosamide

# TUH Status Protocol

- If you cannot get seizures to stop, or have the patient in burst suppression within 2-3 hours, then the urgency of care needs to increase
- **0-5 minutes**
  - ABC's: Maintain adequate airway & oxygenation, monitor hemodynamic status, confirm adequate IV access
  - Blood for labs, check levels
  - ECG

# TUH Status Protocol

## ■ 6–10 minutes

- Thiamine 100 mg; D50 50 mL (unless glucose known)
- Lorazepam: 2 mg increments q 2 minutes while seizing up to a maximum dose of 0.1 mg/kg.
- If rapid IV access not available, give midazolam 10 mg IM, F-PTN (not PTN) IM, or diazepam 20 mg PR\*.

## ■ 10–20 minutes

- Begin F-PTN **20 PE mg/kg** IV at a maximum of 150 mg/min, with blood pressure and ECG monitoring.

## ■ 10–60 minutes

- If seizures persist, start a continuous IV med & cEEG
- Intubation, arterial and central venous access necessary

# Status Management: CIV Meds

## ■ Midazolam

- Load: 0.2 mg/kg; repeat 0.2 mg/kg boluses q 5 - 10 min; max of 1 mg/kg
- Initial rate: 0.05 mg/kg/hr
- Titrate: increments of 0.05 mg/kg/hr until seizures controlled; range: 0.05 – 2 mg/kg/hr
- If still seizing: add or switch to pentobarbital

## ■ Pentobarbital

- Load: 5 mg/kg at 50 mg/min; repeat 5 mg/kg boluses q 30 minutes until seizures stop or burst suppression
- Initial rate: 1 mg/kg/hr
- Titrate: increments of 0.5 mg/kg/hr to burst – suppression; range: 0.5 – 5 mg/kg/hr.

# Barbiturate Blood Level vs. Degree of CNS Depression

Barbiturate	Pentobarbital (µg/ml)	Phenobarbital (µg/ml)
Impaired judgement	$\leq 2$	$\leq 10$
Easily arousable	0.5 – 3	5 – 40
Difficult to arouse	10 – 15	50 – 80
Compatible w/ death in aged or ill	12 – 25	70 – 120
Lethal level	15 - 40	100 - 200

# Status Management: CIV Meds

## ■ Propofol

- Load: 5 mcg/kg/min (0.3 mg/kg/hr) IV infusion for 5 min then titrate in 5 to 10 mcg/kg/min (0.3 to 0.6 mg/kg/h) increments to achieve desired level of sedation / seizure control; allow minimum of 5 min between dose adjustments.
- Initial CIV rate: 5 – 10 mcg/kg/min.
- Titrate in increments of 5 mcg/kg/min until seizures are controlled. Typically achieved without burst – suppression; dose range: 5 – 80 mcg/kg/min.
- If still seizing: add or switch to pentobarbital.

## ■ Propofol is a distant third choice

- Seizure control is hard to maintain

# Status Management

- EEG recommendation:
  - cEEG with a minimum of 24 hours of data collection
  - Infusions may be started without EEG running, but an EEG must be made available ASAP
  - EEG burst general rule: 1 – 2 seconds of ‘burst’ separated by 3 – 8 seconds of suppression (no data to support this).
- Epileptologist consultation
  - Any patient not responding to initial 24 hrs of treatment
- Supplemental seizure control
  - Supplement initial AED
  - Options are many, but prefer IV formulations

# TUH Status Protocol

- Supplemental seizure control:
  - Add to therapeutic F-PTN/ PTN; use IV formulations
- IV LEV\*
  - Load: 1000 mg over 15 min. May repeat x 1
  - Maintenance: 1000 mg every 12 hours.
- IV PB
  - Load: 20 mg/kg IV at 50 mg/min.
  - Maintenance: 3 - 5 mg/kg/day divided into q 12 hrs
- IV VPA
  - Load: 20 – 40 mg/kg over 10 min. If still seizing, give additional 20 mg/kg over 5 min
  - Maintenance: 15-20mg/kg/day divided into q 8 hrs

# Refractory Status

- High dose phenobarbital (levels > 100 gm/ml)
- Pharmacological
  - Ketamine
  - Corticosteroids
  - Inhaled anesthetics
  - Immunomodulation (IVIG or PE)
- Non-Pharmacological
  - Vagus Nerve Stimulation
  - Ketogenic diet
  - Hypothermia
  - Electroconvulsive therapy
  - Surgical management

# Management: Status

- What do you do once status is broken?
  - cEEG, if in burst suppression x 24 – 48 hours with no breakthrough seizures, begin to wean off drip(s).
  - If on multiple drips, wean one drip at a time.
  - Go slow, cEEG to monitor for recurrence of seizures
  - If seizures recur, increase drip to resume burst suppression and add an additional medication.
  - Wait another 48 – 72 hours, then attempt another wean.
- Maintain medications that broke the status with EEG monitoring while adding other medications
  - Maintain therapeutic levels of measurable AEDs
  - Choices to add: VPA, LEV, TPM, etc

# General Management Issues

- If drug levels can be measured, maintain therapeutic levels
  - Be aware of albumin level and renal function, as these can impact on certain AED levels (PHT, VPA).
  - Follow free levels only in patients with low albumin or renal insufficiency.
- Duration of therapy is variable based on diagnosis
- Patients on benzodiazepine or barbiturate drips require close hemodynamic monitoring

# Special Circumstances

- Pregnancy
  - Volume of distribution and clearance of drugs are typically increased
  - Vitamin B6 levels may be low
  - Focus needs to be on stopping seizures. LZP and fos-PHT are recommended as 1<sup>st</sup> & 2<sup>nd</sup> line therapy
- Hypoxic/Anoxic:
  - Prognosis of SE after hypoxic or anoxic insult has been poor, especially with myoclonic SE after cardiac arrest
  - This may need to be reconsidered when therapeutic hypothermia is used

# Summary

- Recognition and description of seizure activity is important to patient care
- Seizures are more common in a Neuro-ICU setting than previously thought
- Seizures may adversely impact outcome
- Status epilepticus is a neurological / neurosurgical emergency

***Special thanks to Dr. Sheetal Malik & the UC Epilepsy Team***

# *Questions?*



<http://www.ucneurocriticalcare.com/physicians>