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 @ 21:00:50
Questions

- Are these seizures?
- Should this be treated?
Given ativan, then loaded with LEV 1000 mg bid
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\textsuperscript{st} / 2\textsuperscript{nd} 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%\(^1^4\)
- New disabling neurological deficits: \(~10\%\)^5
- Some functional deterioration in 23-26%\(^1^2^4\)
- 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
Prognosis: NCSE / RSE

NCSE
- Mortality: 18-52%\textsuperscript{1-3}

RSE
- Mortality: 23-61%\textsuperscript{4-6}

1. Young et al, Neurology 1996
2. Litt et al, Epil 1998
5. Rosetti et al, JNNP 2006
6. Novy et al, Epilepsia 2010
Refractory SE: Prognosis

- Some studies have reported 50% mortality \(^1\)
- 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) \(^2\)

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\(^1\)
  - 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)\(^2\)
  - 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

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

Young & Doig. Neurocritical Care 2005; 2:5-10
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 1st 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

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

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 1st 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
- Cabamazepine (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

<table>
<thead>
<tr>
<th>Barbiturate</th>
<th>Pentobarbital ($\mu$g/ml)</th>
<th>Phenobarbital ($\mu$g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired judgement</td>
<td>$\leq 2$</td>
<td>$\leq 10$</td>
</tr>
<tr>
<td>Easily arousable</td>
<td>0.5 – 3</td>
<td>5 – 40</td>
</tr>
<tr>
<td>Difficult to arouse</td>
<td>10 – 15</td>
<td>50 – 80</td>
</tr>
<tr>
<td>Compatible w/ death in aged or ill</td>
<td>12 – 25</td>
<td>70 – 120</td>
</tr>
<tr>
<td>Lethal level</td>
<td>15 - 40</td>
<td>100 - 200</td>
</tr>
</tbody>
</table>
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\textsuperscript{st} & 2\textsuperscript{nd} 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 / nurosurgical emergency

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

http://www.ucneurocriticalcare.com/physicians