Definition

- Continuous or repeat seizure activity persisting for at least 30 minutes without full recovery between attacks.
- Very few single seizures last for longer than a few minutes – if a seizure lasts for longer than 5 minutes – treat it like status.
Epidemiology

Status epilepticus (SE) is a true neurologic emergency
Mortality rate is 3-26%, morbidity is 10-23%
150,000 annual rate of SE in the US (includes children)
Rates of nonconvulsive status epilepticus (NCSE) – 5-34% of neuro ICU patients
Classification

- Convulsive vs nonconvulsive
- Convulsive seizures involve visible jerking of extremities
- Nonconvulsive seizures involve epileptic brain activity without convulsions
  - May be further classified as simple or partial
  - May be focal or generalized onset
  - In the neuro ICU most seizures are nonconvulsive and would be missed without EEG
Who gets SE?

- The most common risk factor for SE is a history of epilepsy – 22-26% of SE.
  - Risk is 3% per year
- In those with no prior history of epilepsy, the most common cause is stroke – 20%
- In-hospital seizures are frequently related to alcohol or benzodiazepine withdrawal or medication toxicity
Causes

![Graph showing percentages of different causes of epilepsy. Tumor, Trauma, Infection, Unknown, Metabolic, Anoxia, ETOH/drugs, Med change, Stroke.]

Drugs to avoid in seizure patients

- **Antibiotics** – imipenem, fluorquinolones, penicillins and cephalosporins, metronidazole
  - Beta-lactams antagonize the GABA$_A$ chloride channel
  - Pen G – 0.5% risk of inducing convulsions – can precipitate SE
  - Imipenem/cilastatin complex – 1.8-6% risk of inducing convulsions

- **Lithium** – 8-14% risk in Li toxicity

- **Antidepressants**
  - tricyclics and bupropion – medium risk
  - Maprotiline and amoxapine – high risk
Diagnosis of SE

- Convulsions lasting more than 5 minutes
- If the mental status has not ‘improved’ within 30-60 after the end of the episode, NCSE should be considered and a Stat EEG ordered.
- An alteration in level of consciousness in a NSICU patient without alternate explanation – NCSE should be considered
Diagnosis

- Serum neuron-specific enolase – may be normal after a single seizure. Tends to be elevated in SE+NCSE even with no obvious concomitant brain injury – not currently in clinical use

- Serum prolactin – One study of 200 people presenting with seizure: sens -42%, spec -82%, PPV - 74%, NPV - 54%. Not that useful as a diagnostic tool but may be useful as a confirmatory test
Beginning of a focal seizure

FIGURE 6 -6 Start of typical seizure from left posterior quadrant.

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Start of generalized tonic-clonic seizure

FIGURE 6 - Transition from absence status epilepticus to a generalized tonic-clonic seizure.
Absence Status Epilepticus

FIGURE 6 - Absence status epilepticus.
Left hemispheric seizure

FIGURE 6-7 Middle of seizure, almost 2 minutes after EEG 1, now involving entire left hemisphere.
Left hemispheric seizure

FIGURE 6 - 7 Middle of seizure, almost 2 minutes after EEG 1, now involving entire left hemisphere.
Spread of right NCSE to left hemisphere

FIGURE 6-10 Continuation of seizure, remaining maximal on the right but spreading to the left.
Morbidity

- Convulsive seizures can result in hyperthermia, acidosis, rhabdomyolysis, aspiration and trauma.
- The longer the seizure, the greater risk of cerebral damage due to: excitotoxicity, apoptosis (due to increased intracellular $\text{Ca}^{2+}$), and epileptogenic synaptic reorganization.
- Prolonged seizures can be seen on DWI sequence on MRI.
Cortical Laminar Necrosis

- Can be the result of anoxia, status epilepticus, chemotherapy or ‘cerebral’ hypoglycemia
Treatment

- Treatment of SE needs to be initiated rapidly – the longer it takes to get the seizures under control, the harder it is to control them at all.
- First-line medications control SE in 80% of patients if given within the first ½ hour, but only 40% if started after 2 hours.
- Look for an underlying cause:
  - Labs, drugs, imaging, LP
Initial Assessment

- Like any emergency patients – ABCs first
  - Assess airway, breathing and circulation
  - Oxygen
  - glucose check
  - IV access
  - labs – chemistry (including Mg, Ca), CBC, troponin, renal and liver function, AED levels, toxicology screen
  - ABG
Next step in treatment

- Give thiamine and dextrose if glucose is unknown or low.
- Give lorazepam 4 mg IV – repeat in 5 minutes if seizure persists
  - If no IV access – diazepam 20 mg PR (Diastat), midazolam 10 mg intranasally, buccally or IM
- If still seizing – IV fosphenytoin 20 mg/kg at 150 mg/min
  - Must be done with blood pressure and EKG monitoring
Next step in treatment

- If still seizing – intubate – except for valproate – and one of the following options
  1) midazolam: load 0.2 mg/kg – bolus 0.2-0.4 mg/kg q5m until sz stop or max of 2.9 mg/kg – then gtt at 0.1 mg/kg/h (0.05-2.9)
  2) propofol: load 1-2 mg/kg – bolus 1-2 mg/kg q3-5m until sz stop or max of 10 mg/kg then gtt 2 mg/kg (1-15)
  3) phenobarbital: load 20 mg/kg at 50-100 mg/min
  4) valproate: load 40 mg/kg over 10m – if sz persist, then 20 mg/kg over 5 min
Next step in treatment

- If still seizing – pentobarb gtt
- Load 5 mg/kg at 50 mg/m, 5 mg/kg boluses until sz stop.
- Gtt rate 1 mg/kg/h (0.5-10)
  - Titrate to burst suppression (? vs seizure control)
- EEG monitoring for any continuous IV treatment or if patient doesn’t awaken rapidly
How aggressive?

- The standard used to be burst suppression
- Rosetti review of 49 episodes of SE – no difference in outcome regardless of degrees of suppression or AED used
- NCSE – still uncertain how aggressively to treat (especially PLEDS)
Benzodiazepines

- First-line treatment for seizures
  - Lorazepam (Ativan)
  - Midazolam (Versed)
  - Diazepam (Valium)
- Facilitate GABA receptors leading to post-synaptic hypoexcitability
Lorazepam

- Loading dose – 4-8 mg/ 0.1 mg/kg
- Onset of action - 3-8 minutes
- Duration of effect - 4-6 h
- Elimination half-life – 14 hours
- Effects: sedation, respiratory depression, hypotension
Midazolam

- Loading dose – 0.05-0.2 mg/kg
- Onset of action - less than a minute
- Elimination half-life – 2-4 hours
- Less hypotension than lorazepam, significantly longer ½ life noted in critically ill patients on a gtt.
Diazepam

- Loading dose – 0.1-0.4 mg/kg
- Onset of action - 20 seconds
- Duration of effect - 5-10 minutes
- Elimination half-life – 20 hours/96 hours
- Lipid soluble with rapid tissue redistribution – effective seizure control for 5-10 minutes but sedative effect very prolonged due to hepatic intermediate production
Phenytoin

- Inhibits high-frequency firing by blocking voltage-dependent sodium channels
- Load 20 mg/kg – max rate 50 mg/min
- If seizures continue, may re-load with 5-10 mg/kg
- Onset of action – 20-25 minutes
- Goal level 20-25 total or 2-2.5 free
- Must be on a monitor when loading – can cause heart block
- P450 inducer and protein bound – many drug interactions
- Cannot be mixed with glucose given IM, should not be given via peripheral IV
Fosphenytoin

- A phenytoin prodrug - dephosphorylates quickly to phenytoin
- Dosed in “PE” – phenytoin equivalents – e.g mg PE
- Same dosing and serum levels but can be given more rapidly – 150 mg/min
- As with phenytoin – can be reloaded if seizures continue – 5-10 mg/kg
- Can be given IM or via smaller veins
Valproic acid

- Works via Na channel inhibition and GABA facilitation
- Not FDA approved for SE – however studies have shown benefit
  - Misra 2006 – VPA vs PHT – 66 vs 42% seizures aborted in GTC
  - If first agent failed – second agent used – VPA vs PHT as 2nd agent – 79% vs 25%
- Preferably used for GTC and myoclonic SE; may be used for focal onset SE, absence SE
- Good for the SE patient with “DNI” status
Phenobarbital

- GABA potentiation
- Load with 15-20 mg/kg, max infusion rate 50-100 mg/min
- Elimination half-life – 72 hours
- Target level 30-45 mcg/ml
- Significant respiratory – especially with benzos - intubate
- Avoid in liver disease
- May cause Stevens-Johnson syndrome
Propofol

- GABA agonist, NMDA inhibitor, slow calcium channel modulator
- Load 1 mg/kg – max load 10 mg/kg, gtt 2 mg/kg (1-15)
- Rates of >5 mg/kg/h for >48 h – increased risk of propofol infusion syndrome
- Avoid in those on carbonic anhydrase inhibitors (Diamox, Topamax, Zonisamide) – can cause refractory acidosis
Propofol Infusion Syndrome

- Due to large, prolonged doses of propofol – has occurred after single doses in pediatric patients
- Lactic acidosis, rhabdomyolysis, cardiovascular collapse, frequently lethal (80%)
- Monitor lactic acid and CK levels, change gtt if on high dose propofol gtt for several days
Pentobarbital

- GABA agonist
- Load 5 mg/kg to max 25-50 mg/kg, gtt at 1 mg/kg (0.5-10 mg/kg/h)
- Elimination half-life – 15-60 hours
- Can remain comatose for days after infusion stopped
- Causes hypotension and myocardial depression requiring support
- Risk of ileus, immune suppression and Stevens-Johnson syndrome
Levetiracetam

- Not FDA approved for use as a monotherapy for epilepsy or for SE
- SV2A receptor inhibitor
- Knake et al. – 18/18 patients had benzodiazepine refractory SE controlled with levetiracetam, 17/18 avoided intubation
- Ruegg et al. – 16/24 ICU patients with SE successfully terminated
- Load 1-2 g, maint 2-4 g/d – insufficient evidence to recommend use
Refractory Status Epilepticus

- Seizures not stopped by the use of one first line and one second line agent
- Either clinical or electrographic seizures
- Mortality approaches 50%, few return to premorbid baseline
RSE

- Two goals – stop seizures and get them on a regimen that will control their seizures when they are no longer on a drip
- Agents useful for stopping RSE that require intubation
  - propofol, pentobarbital, IV midazolam/lorazepam,
  - Rarely: inhaled anesthetics (isoflurane, desflurane), hypothermia
Criteria for NCSE

- At least 10 seconds of one of the following
- Primary criteria
  - 1) generalized or focal spikes, sharp waves, sharp and slow waves or spike and slow waves at ≥3/s
  - 2) above at ≤3/s and secondary criteria
  - 3) sequential, periodic or quasi-periodic at ≥1/s with evolution in frequency, location or morphology
- Secondary criterion
  - Significant improvement in clinical appearance or return of normal EEG pattern (e.g. PD alpha) associated with AED use
Are they seizing?

- They have unusual EEG activity but no convulsions – do a benzo trial
- Must be in a monitored environment – on EEG, tele, pulse ox and dedicated nurse
- Small doses or benzos – e.g. midazolam 1 mg – clinical and EEG check between doses
- Stop trial if:
  - EEG improves persistently
  - Patient improves clinically
  - AE such as resp depression or hypotension
  - Max dose given – e.g. midazolam 0.2 mg/kg
- Equivocal if EEG improves but pt does not
PEDS

- PEDS = periodic epileptiform discharges
  - PLEDS = periodic lateralized epileptiform discharges
  - GPEDS = generalized epileptiform discharges
  - BiPLEDS = bilateral periodic lateralized epileptiform discharges
End of seizure followed by PLEDs

FIGURE 6 - End of seizure, 1 minute after EEG 2. After seizure offset, seizure activity is replaced by periodic lateralized epileptiform discharges recurring at just under 1 per second, also maximal in the left posterior quadrant.

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Weaning in RSE

- If a patient required a continuous drip to control their seizures, they should be on EEG:
- Ensure they are on at least one AED and levels are therapeutic (if applicable)
  - Phenytoin, levetiracetam, topiramate, valproate, phenobarbital
- Titrate drip off slowly 12-24 h after seizures controlled
- Restart drip if seizures recur, treat for longer then try slower taper; ensure optimal AED levels
- Starting pts on phenobarbital may help wean pentobarbital drip
Novel Treatment of SE

- Ketamine - ?dose – anesthetic dose =
  - 1 - 5 mg/kg, with infusion of 1 – 5 mg/kg/hr (20 - 80 mcg/kg/min)
  - Give with benzo – decrease later psych effects.
- Topamax – has worked via NG – dose 300-1600 mg
- Vimpat – single case study of 5th drug – SE tx with 300 mg
- Keppra – 65-69% of SE terminated. Bolus 500mg-2g, mean dose 3g/d – less successful with: dose of >3g/day, no loading dose, age over 80, delay >48 h, NCSE with coma.
  - Effective in pediatric sz/SE in critically ill
- Verapamil - ?AED vs alteration of free AED levels
- Magnesium: as a Gtt similar to use in eclampsia
- Hypothermia – 4pts, goal temp 31-35
- Ketogenic diet – has worked in some adults with RSE
- ECT – worked for 2 of 3 pts with RSE