Diagnosis and Management of Status Epilepticus

Alfred T. Frontera Jr., MD
Asst. Professor of Neurology
University of South Florida
Director, Epilepsy Center of Excellence
James A. Haley VA
Tampa, Florida

Disclosures:

- None.

Learning Objectives:

- Identify the various types and causes of status epilepticus (SE).
- Understand the role of continuous EEG (cEEG) in the diagnosis and management of SE.
- Be familiar with the current recommendations for the treatment of SE.

SE Definition:

- OLD: Continuous seizure activity persisting >30 minutes or repetitive seizures without recovery of consciousness between attacks.

- NEW: Seizures that persist for > **5 minutes** or repetitive seizures without recovery between attacks.

- PRACTICAL: If you have time to get lorazepam and seizure is still going, GIVE IT!!

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Special Article

It's Time to Revise the Definition of Status Epilepticus

Daniel H. Lowenstein, *Thomas Bleck, and †Robert L. Macdonald

*Department of Neurology and Anatomy, University of California–San Francisco, San Francisco, California; *Department of Neurology, University of Virginia Medical Center, Charlottesville, Virginia, and †Department of Neurology, University of Michigan, Ann Arbor, Michigan, U.S.A.*

Why this Revision?

- Most szs will spontaneously terminate in 1-2 minutes.
- Szs persisting longer than this implies failure of physiologic factors that normally terminate szs.
- Szs that persist for >5-10 mins are unlikely to terminate without intervention. (1,2)
- Duration of szs prior to tx is a key determinant of treatment success and mortality (3,4,5,6)

- 1. Jenssen, et al. Epilepsia 2006;47:1499-1503. 2. Sinnar et al. Ann neurol 2001;49:659-64. 3. Treiman et al. Epilepsia 1984;25:653. 4. Young, et al. Neurology 1996;47:(1): 83-89. 5. Lowenstein et al. Neurology 1993;43 (3 pt 1):483-488. 6. Lowenstein et al. N Eng J Med 1998;338(14):970-976.

SE Classification (Based on Semiology):

- Convulsive:
  - Tonic-Clonic
  - Tonic
  - Clonic
  - Myoclonic
  - Atonic
  - Partial Motor (Epilepsia Partialis Continua)
- Non-convulsive:
  - Absence
  - Atypical Absence
  - Complex Partial
  - Simple Partial (Aura continua)

SE Classification (Based on Etiology):

- Acute Symptomatic
- Remote Symptomatic
- Idiopathic

Epidemiology of SE:

- Incidence: ~100,000-200,000 cases in US/year.
- Bimodal peak in children (<1 yr) and older adults (>60 yrs).
- NCSE is likely under-diagnosed.
- High Mortality (up to ~30%).
- High Morbidity (~10-23%).

Potential Etiologies of SE:

- **Pre-existing Epilepsy:**
  - breakthrough seizures or med non-compliance/discontinuation of meds.
- **Structural Lesion (old or new):**
  - trauma, tumor, AVM, infarct, bleed (SDH, EDH, SAH)
- **Metabolic Derangements:**
  - uremia, hypo or hyperglycemia, hyponatremia, hypo or hypercalcemia, hypokalemia, hypomagnesemia
- **Drug Toxicity/Withdrawal:**
  - cocaine, TCA's/ETOH, benzodiazepines, barbiturates, opioids)
- **CNS infection:**
  - meningitis, encephalitis, abscess
- **Hypoxia (cardiac arrest)**

Pathogenesis:

- Persistent cellular excitation (glutamate/NMDA mediated)
- Failure of suppressing mechanisms (GABA mediated)
- GABA (endocytosis) and NMDA (exocytosis) transmission implicated in sustained seizure activity.

Generalized Convulsive SE:

- Most common.
- Consists of continuous clonic and/or tonic motor activity.
- May be asymmetric.
- May be subtle clinically (nystagmus, mouth/eye/face twitching) despite generalized seizure activity on EEG (electro-clinical dissociation).

Convulsive SE: Prognosis

- Varies by age, etiology and duration.
- 2-3% mortality in children
- >30% mortality in adults.
- Anoxic injury has highest mortality, AED withdrawal or non-compliance has lowest.
- Increased mortality associated with:
  - Age
  - Seizure duration (>1 hour associated with increased mortality).
  - Etiology (anoxia is worst).

SE Mechanism of Injury:

- **Neuronal Injury:** most research supports irreversible neuronal damage at 60 mins.

- Proposed Mechanisms:
  - **Excitotoxicity** (release of glutamate and aspartate, increased intracellular Ca+2 through NMDA receptor activation)

  - **Hypoxia/Ischemia:** increased metabolic demands-> CBF maintained early (catecholamine surge) but drops off later.

SE Mechanism of Injury:

- **Systemic Effects:**
  - **Cardiovascular:** tachycardia, arrhythmias, hypotension, MI.
  - **Respiratory:** Hypoxia/CO2 Retention, Pulmonary Edema, Aspiration Pneumonia
  - **Renal:** Rhabdomyolysis, myoglobulinemia, acute tubular necrosis
  - **Autonomic:** hyperpyrexia, impaired cerebral autoregulation.
  - **Metabolic:** lactic acidosis, hypoglycemia, hypokalemia, hyponatremia.
  - **Neurologic:** Increased ICP, decreased cerebral perfusion, cerebral edema.

SE Morbidity:

- Respiratory failure and its complications
- Cardiac Arrythmias->stroke, MI.
- Acute Renal Failure
- Infection
- Risk of Epilepsy
- Risk of recurrent SE
- Permanent neurological deficits (behavioral and neurocognitive effects)

SE: Key Points in History

- **Seizure Semiology:**

  -Detailed description is key. i.e. any lateralizing or localizing features such as gaze deviation, face or extremity jerking, posturing, automatisms, altered mental state, etc.)

- **Seizure Duration:**

  -When was the pt last seen normal? What was the duration of convulsive activity? What was the duration of altered mental status? (to help determine post-ictal vs nonconvulsive state).

- **PMH:**

  -Attention to possible precipitators of SE- epilepsy or epilepsy RF (head trauma with LOC, CNS infxn., febrile szs, family hx), hx of structural brain lesions, immunocompromised, DM or hypoglycemia, etc.

SE: Key Points in History

- Medications:

  -If hx of epilepsy get current AEDs and doses and attempt to determine compliance.

  -Review for medications that can lower seizure threshold (antibiotics, TCA's, etc).

- Social Hx:

  -attention to ETOH, Illicit drug use.

SE: Key Points in PE

- Full Neurological Exam is crucial!!
- Focal Exam findings such as Todd's Paralysis or Todd's equivalents such as aphasia, numbness, etc. indicate a potential focal brain lesion
- Positive Localizing Symptoms:
  - Clonic/twitching/tonic movements
  - Eye deviation
  - automatisms
  - Pay attention to subtle signs such as blinking, face/mouth twitching, nystagmus.
- Negative Localizing Symptoms:
  - Aphasia (Motor or Expressive), neglect, apraxia, field cut.

SE: Key Points on PE

- Mental Status:
  - Pts with generalized convulsive SE should awaken gradually after seizures disappear.
  - If mentation fails to improve 20 mins after last convulsive activity was observed or if mentation remains abnormal 60 minutes after cessation of convulsions…this is NCSE until proven otherwise.
  - Need treatment trial or urgent EEG to clarify situation.

SE: Differential Dx

- Movement Disorders (myoclonus, asterixis, tremor, chorea, tics, dystonia)
- Herniation (decerebrate or decorticate posturing).
- Psychiatric Disorders (PNEA, Acute Psychosis, Catatonia).
- Sympathetic Storm
- Limb-shaking TIA's
- Convulsive Syncope
- Toxic-Metabolic Encephalopathy (for ?NCSE pts)
- Postictal State (for ?NCSE pts)

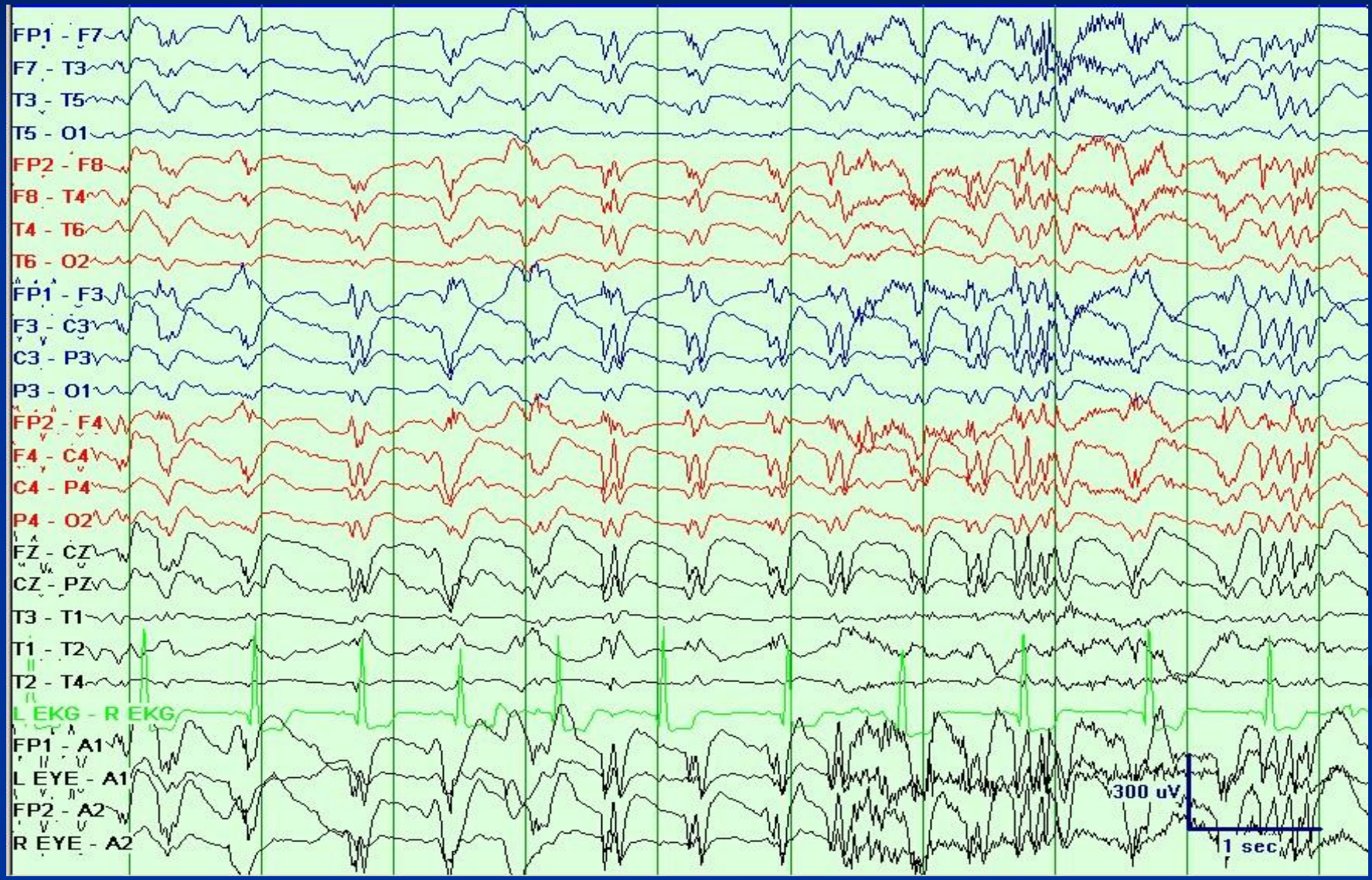
Making the Diagnosis:

- Convulsive SE
  - Diagnosis is usually obvious (at least initially)
  - EEG is usually NOT needed to make the correct diagnosis
  - Do NOT delay treatment waiting for an EEG
- NCSE
  - Can be difficult to diagnose
  - Common presentation: "altered mental status"
  - Requires EEG to make the diagnosis

Clues in Identifying NCSE

- Unexplained encephalopathy, especially in patients with risk factors for seizures
- Subtle jerking of the extremities and face (large cortical representation)
- Abnormal eye movement or eye deviation

Sample EEG in NCSE:



Continuous EEG (CEEG):

- What is continuous EEG (cEEG)?
  - EEG recorded for hours, days, etc +/- video
  - More readily available now due to:
    - Digital EEG
    - Increased computer memory
    - Remote access

Uses of CEEG:

- 1. Identify subtle or non-convulsive sz activity.
- 2. Differentiate szs from non-epileptic events
- 3. Monitor response to treatment
- 4. Suggest etiology and/or prognosis (i.e. HSV, anoxia)

Uses of CEEG: Identify Subtle or NCSE

- After convulsive sz or SE if patient does not rapidly return to baseline MS -> CEEG!
  - MS (should show signs of improvement within 20 mins and recovery within 60 mins)
  - Up to 50% of pts with generalized convulsive szs will have NCSE after clinically apparent convulsive activity has stopped.
  - Pts with NCSE after CSE have 2x's mortality of those with CSE only.

Uses of CEEG: Identify Subtle or NCSE

- *Unexplained* mental status changes -> CEEG
  - Up to 1/3 of NICU pts will have nonconvulsive seizures (and most of these will be in NCSE)
  - Up to 10% of MICU pts will have nonconvulsive seizures.
- Pts who are pharmacologically paralyzed

->CEEG

Uses of CEEG: Szs or Not?

- Characterization of spells commonly encountered in the ICU
  - Tremors, rigidity, posturing, agitation, chewing, etc.
  - Changes in BP or HR (Szs vs PAIDs)

Other Uses of CEEG:

- Neurotelemetry:
  - Detection of ischemia in stroke pts
  - After SAH (early detection of vasospasm, increased ICP)

How Long Should We Monitor?

- 24 hours of cEEG monitoring detects ~95% of szs in non-comatose pts
- 48 hours of cEEG monitoring detects ~93% of szs in comatose pts
- Medically induced coma → continuous EEG recording until medications are weaned off.

Pitfalls of CEEG:

- Labor intensive
  - Technician (not in-house)
  - Physician (remote-access)
- May delay other procedures (MRI, CT)
  - MRI compatible leads not widely available

Pitfalls of CEEG:

- Large quantity of data to interpret
- Artifacts can be misinterpreted
  - Performing video with cEEG helps

SE: Work-Up

- Labs:
  - Fingerstick glucose.
  - Cbc, chem 7, Ca++, Mg+, PO4-, LFTs, troponin, ABG, UA, Urine Toxicology, AED levels.
- Lumbar Puncture:
  - If febrile, immuno-compromised, no other clear etiology.
- Imaging:
  - Head CT emergently
  - MRI later.
    - Sz focus may show up on Flair or DWI/ADC in SE

SE Treatment:

- GOALS:
- 1. Abort all clinical and electrographic seizures.
- 2. Maintain vital functioning (may require intubation, ICU monitoring).

SE Treatment:

- Crucial not to delay treatment!!!
- Longer you wait the more difficult SE is to treat.
- ~80% of pts respond to first line meds if started within 30 minutes of onset of SE.
- <40% respond if treated within 2 hours.
- Mortality increases with prolonged SE >1-2 hours.

- Status Epilepticus Treatment Protocol:

(**adapted from Columbia University/NYPH Generalized Convulsive Status Epilepticus Treatment Algorithm in Adults 2010)

Step 1: 0-5 minutes

- ABCs (give nasal O2, intubate if necessary)
- Begin continuous physiologic monitoring (O2 Sat, HR, BP, EKG)
- Obtain IV Access
- Diagnose Underlying Cause (Focused Hx and PE)
- Obtain fingerstick glucose then CBC, BMP, Ca++, MG+, PO4-, LFTs, troponin, ABG, urinalysis, urine toxicology, ETOH levels, AED levels (phenytoin, valproate, carbamazepine).

Step 2: 5-10 minutes

- Thiamine 100 mg IV
- 50 mL D50W IV unless glucose level is known and not low.
- Lorazepam 2-4 mg IV over 2 mins, if still seizing repeat (up to 8 mg).
- If no rapid IV access give diazepam 20 mg PR* or midazolam 10 mg intranasally, buccally or IM**

Notes:

*IV diazepam can also be given PR if rectal formulation is not available.

**IV midazolam may be given by any of these routes.

Step 3: 10-20 minutes

- **Begin fosphenytoin 20mg PE/Kg IV** at rate of up to 150 mg/min. (conversion t1/2 to phenytoin is ~15 minutes).
- If fosphenytoin is unavailable give **phenytoin 20 mg/Kg IV** at rate of up to 50 mg/min.
- Side Effects: **Hypotension, arrhythmias.**

  -phlebitis and tissue necrosis seen with phenytoin.
- Note: If Szs persist, can skip right to Step 4 or can perform Step 3 simultaneously with Step 4 in which case rate of infusion of PHT/fos-PHT should be slowed.

Step 4: 10-60 minutes

- If szs persist, now you are dealing with **Refractory SE (RSE) (~30% of cases).**
- Give one of the following:
  - 1. **Continuous IV Midazolam (Versed):**
  - 2. **Continuous IV Propofol (Diprivan):**
  - 3. **IV Valproate**
  - 4. **IV Phenobarbital**
  - Note: Intubation +/- IV pressors may be necessary at this step!

SE Tx: Midazolam

- 1. **Continuous IV Midazolam (Versed):**
  - load 0.2 mg/Kg IV over 2-5 mins, repeat q 5 mins until szs stop up to max of 2 mg/Kg)
  - **Bolus is the key to stopping SE**
  - Initial rate=0.1mg/Kg
  - Maintenance rate=0.05-2.9 mg/Kg/hr
  - Side Effects=**Hypotension**
  - **Tachyphylaxis**
  - Accumulates in fat tissue

SE Tx: Propofol

- 2. **Continuous IV Propofol (Diprivan):**
  - load 1-2 mg IV over 3-5 mins, repeat q 3-5 mins until szs stop up to max of 10 mg/Kg.
  - Initial rate=2 mg/Kg/hr (33 mcg/Kg/min)
  - Maintenance rate=1-15 mg/Kg/hr (17-250 mcg/Kg/min)
  - Side Effects= hypotension, hypertriglyceridemia, pancreatitis,
  - **Propofol Infusion Syndrome: metabolic acidosis, lipemia, bradyarrythmia-> cardiac arrest, rhabdomyolysis->renal failure, DEATH.**
    - **More common in children.**
  - Monitor pH, bicarbonate, CPK and cardiac fxn.
  - Accumulates in fat tissue.
  - Contraindications: allergy to soy, egg.
  - Avoid doses >5 mg/Kg/hr (88 mcg/Kg/min) for >24-48 hrs.

- Note: Intubation +/- IV pressors may be necessary at this step!

SE Tx: Valproate

- 3. **IV Valproate (Depacon):**
  - NOT FDA approved for tx of SE
  - load 40 mg/Kg IV over 10 mins; if still seizing an additional 20 mg/Kg over 5 mins (max rate of 6 mg/Kg/min).
  - Initial dosing: 1 gram IV q 6 hrs.
  - Infusion dose range: 2-12 mg/Kg/hr
  - Side Effects: tremor, **thrombocytopenia**, platelet dysfunction, low fibrinogen, **encephalopathy, hepatic toxicity, hyperammonemia encephalopathy**, pancreatitis.
  - Goal level: 80-140 mg/L. Free=4-11 mg/L.
  - **May be AED of choice for SE in patients with Idiopathic Generalized Epilepsy (IGE).**

- Note: Intubation +/- IV pressors may be necessary at this step!

SE Tx: Phenobarbital

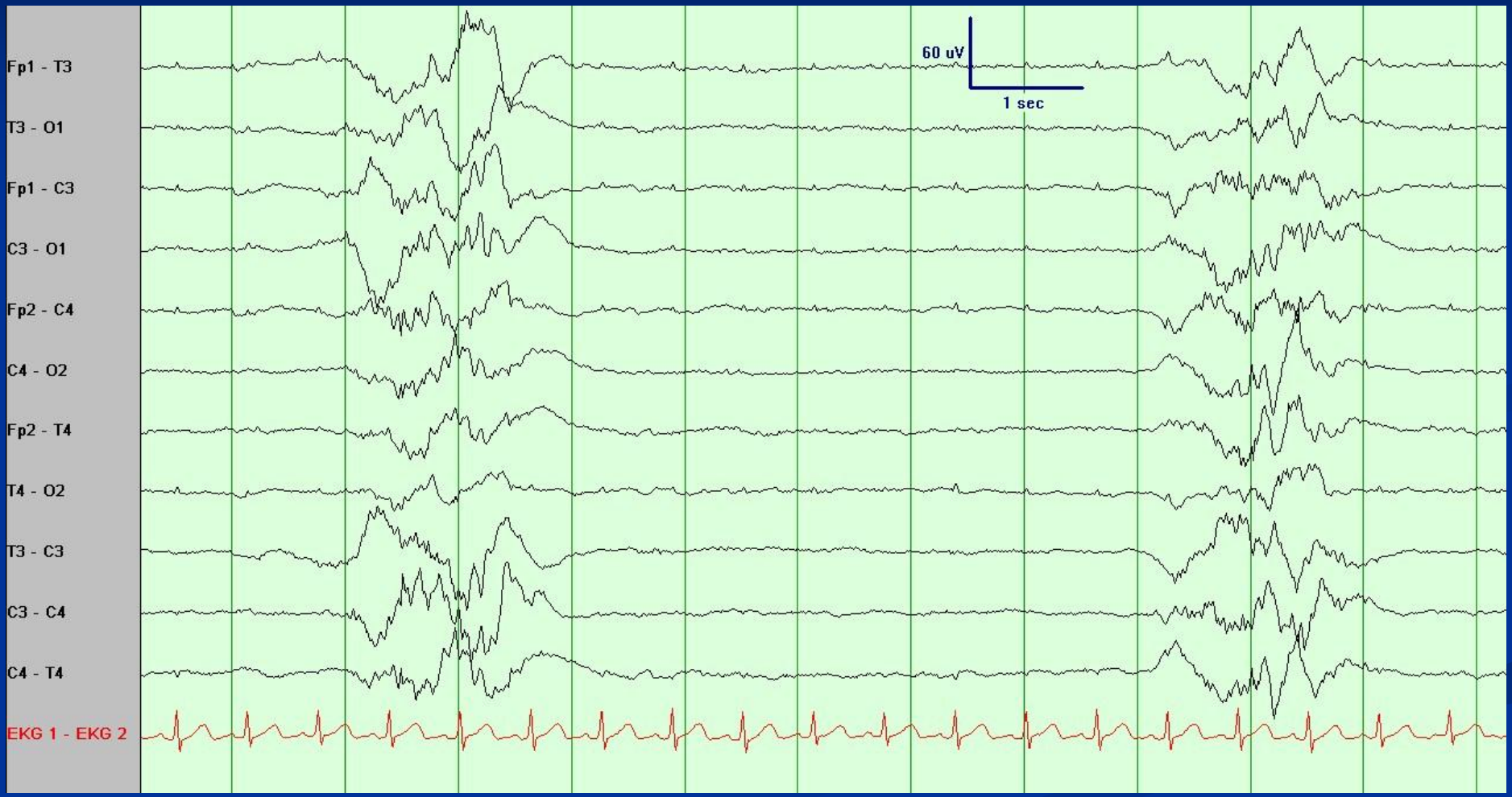
- 4. **IV Phenobarbital (Luminal):**
  - load 20 mg/Kg IV at rate up to 60 mg/min.
  - Maintenance: 1-3 mg/Kg/day divided in 2-3 doses.
  - **Side Effects: Hypotension, hypoventilation, metabolic acidosis (due to porpylene glycol)**
  - Goal Level: 20-50 mg/L

- Note: Intubation +/- IV pressors may be necessary at this step!

Step 5: >60 minutes

- If seizures persist, start **continuous IV Pentobarbital (Nembutal):**
  - Load 5 mg/Kg IV up to rate of 50 mg/min; repeat 5 mg/Kg boluses until seizures stop.
  - Initial rate: 1 mg/Kg/hr
  - Maintenance rate: 0.5-10 mg/Kg/hr titrated to suppression burst on EEG.
  - Side Effects: **Hypotension, gastric stasis, myocardial suppression, thrombocytopenia, metabolic acidosis (diluted in propylene glycol).**
  - Goal level: Hypnotic 1-5 mg/L; Coma 10-50 mg/L

Step 5: Burst Suppression



What degree of suppression?

- Unknown, no clear evidence of better outcomes with seizure suppression vs burst suppression vs "isoelectric" suppression.

How Long to Suppress?

- Unclear
- Minimum of 24 hours
- Longer periods if 24 hr suppression fails

SE Treatment-Other AEDs:

- Levetiracetam (Keppra):
- NOT FDA approved for tx of SE.
  - Load: 2.5 grams IV over 5 mins (1-4 grams over 15 mins)
  - Initial 3-6 grams/day in 3-4 divided doses
  - Maintenance: 2-12 grams/day IV/PO in 3-4 divided doses.
  - **Must renally adjust dosing:**
    - HD: 50% removed by HD; dose q 12 hours and add 50% of AM dose to PM dose on day of dialysis.
  - **May be AED of choice in SE pts with hepatic failure.**

SE Treatment-Other AEDs:

- Lacosamide (Vimpat):
  - NOT FDA approved for tx of SE
  - Load: 300 mg IV over 30 mins
  - Maintenance: 200-300 mg IV over 30-60 mins q 12 hrs
  - Side Effects: may prolong PR interval.

SE Treatment-Other AEDs:

- Ketamine (Ketalar):
- NOT FDA approved for tx of SE
  - Load: 1.5 mg/Kg q 3-5 mins until szs stop up to max of 4.5 mg/Kg.
  - Initial rate: 1.2 mg/Kg/hr (20 mcg/Kg/min), bolus and increase rate by 10-20 mcg/Kg/min until sz control.
  - Maintenance: 0.3-7.5 mg/Kg/hr (5-125 mcg/Kg/min)
  - NMDA receptor antagonist.
  - **Caution in pts with cardiac disease, hypertension or increased ICP.**
  - Consider combining with benzodiazepines to lower dose requirements.

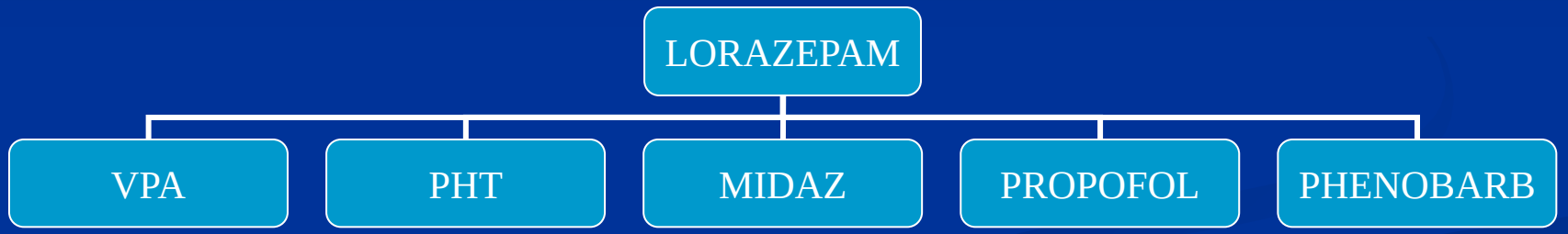
SE Treatment: Final Notes

- Last Resort Options:
- *Note: NOT FDA approved
  - IV Steroids/IVIG or Plasma Exchange
  - Vagal Nerve Stimulation (VNS)
  - Transcranial Magnet Stimulation (TMS)
  - Electroconvulsive Therapy (ECT)
  - Hypothermia
  - Resective Surgery (Focal Resection, Sub-Pial Transections)

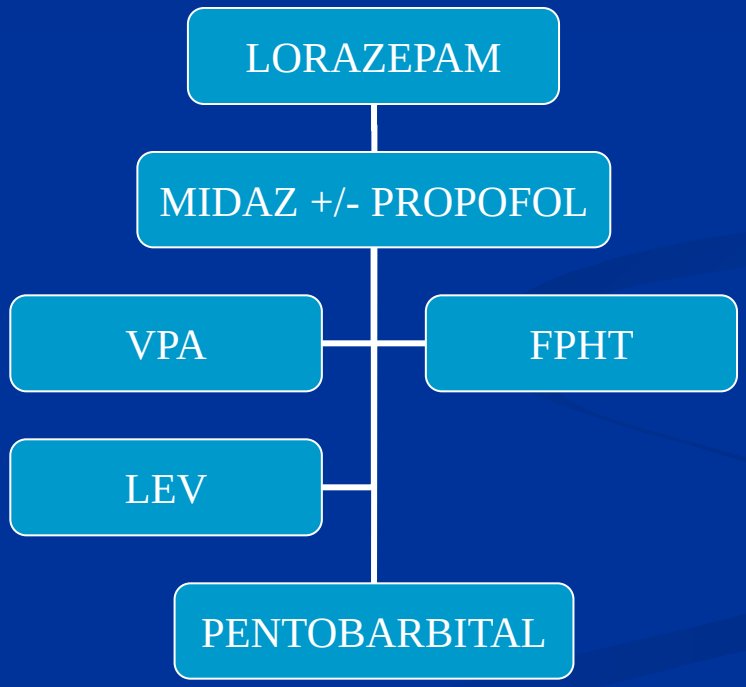
SE Treatment: Final Notes

- Following slides courtesy of J. Lawrence Hirsch, MD (Yale University).

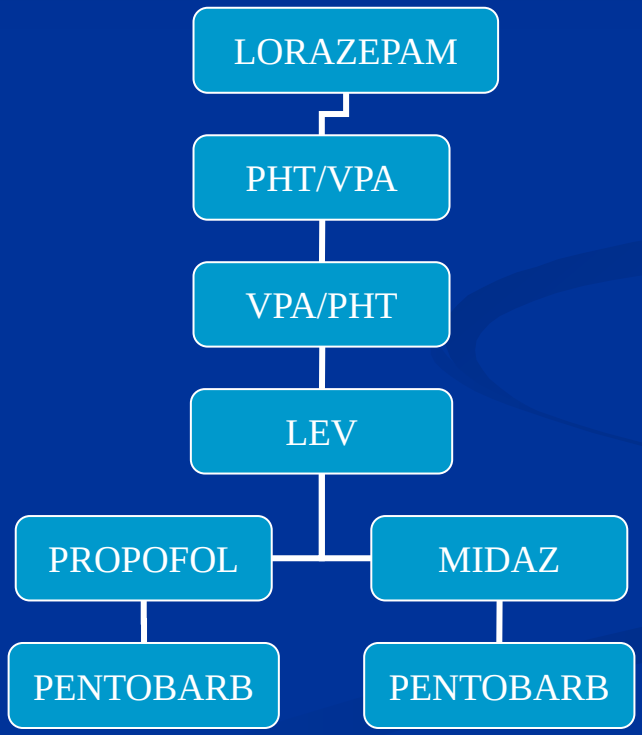
EQUAL OPPORTUNITY APPROACH



TERMINATOR APPROACH



MISS DAISY APPROACH



SE Treatment: Final Notes

- STAT EEG monitoring if pt does not rapidly awaken or if any continuous IV treatment is used!
- Head CT prior to cEEG hook up.
- Evaluate for toxic-metabolic etiologies and correct them.
- Correcting underlying toxic-metabolic derangements is more effective than administering AEDs!!

Conclusions:

- SE is common
- SE is potentially life threatening
- NCSE should always be considered in coma of "unknown origin"
- cEEG has an important role in the ICU
- cEEG has limitations
- Early identification and treatment is paramount!!!

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