

Status Epilepticus:

The good, the bad, the ugly

Emily J. Gilmore, MD, MS

Assistant Professor

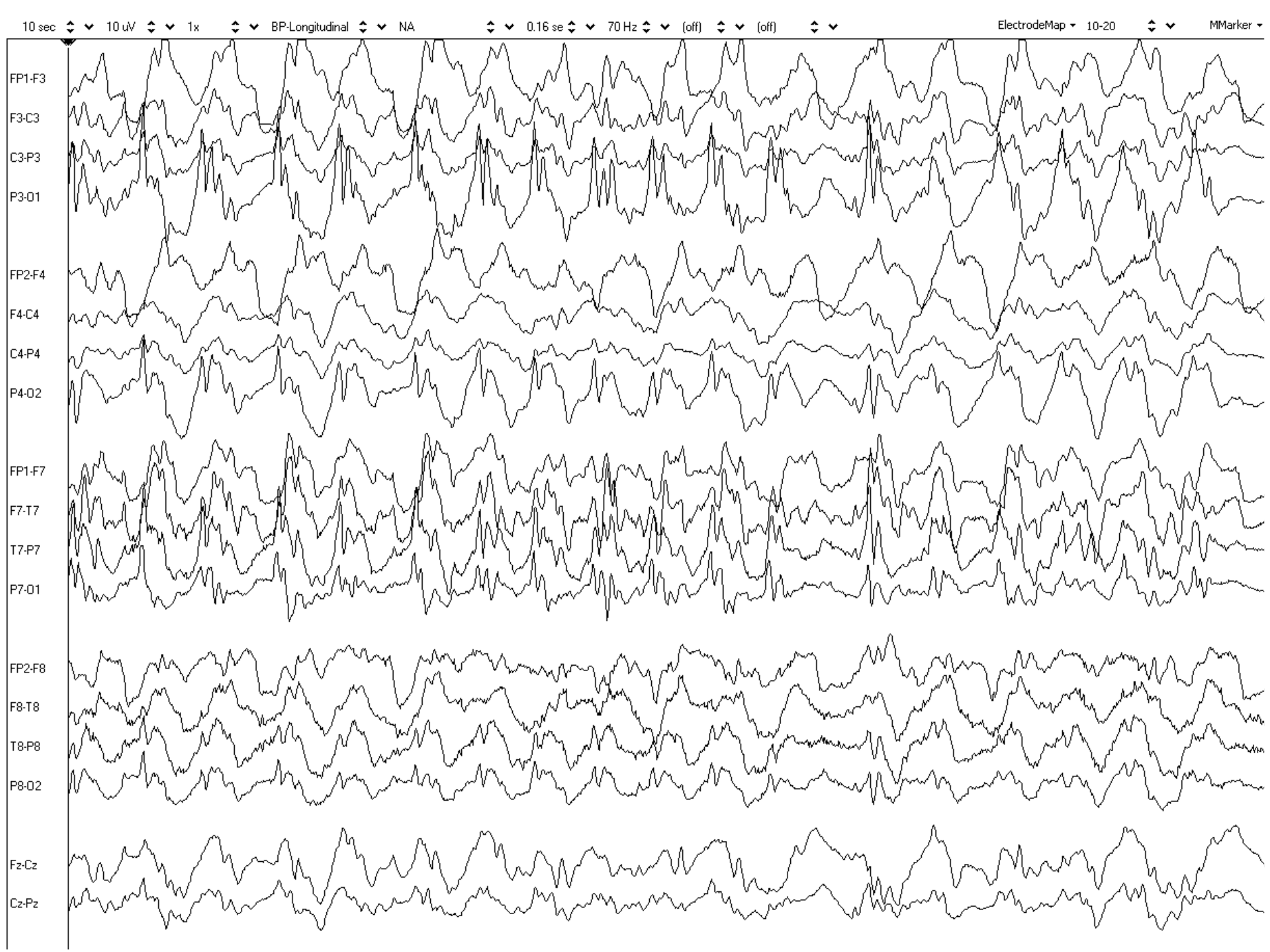
Division of Neurocritical Care and Emergency Neurology, and Epilepsy (CCEEG)

Yale New Haven Hospital/Yale School of Medicine

Latin American Workshop

Havana, Cuba

November 14th -15th 2016



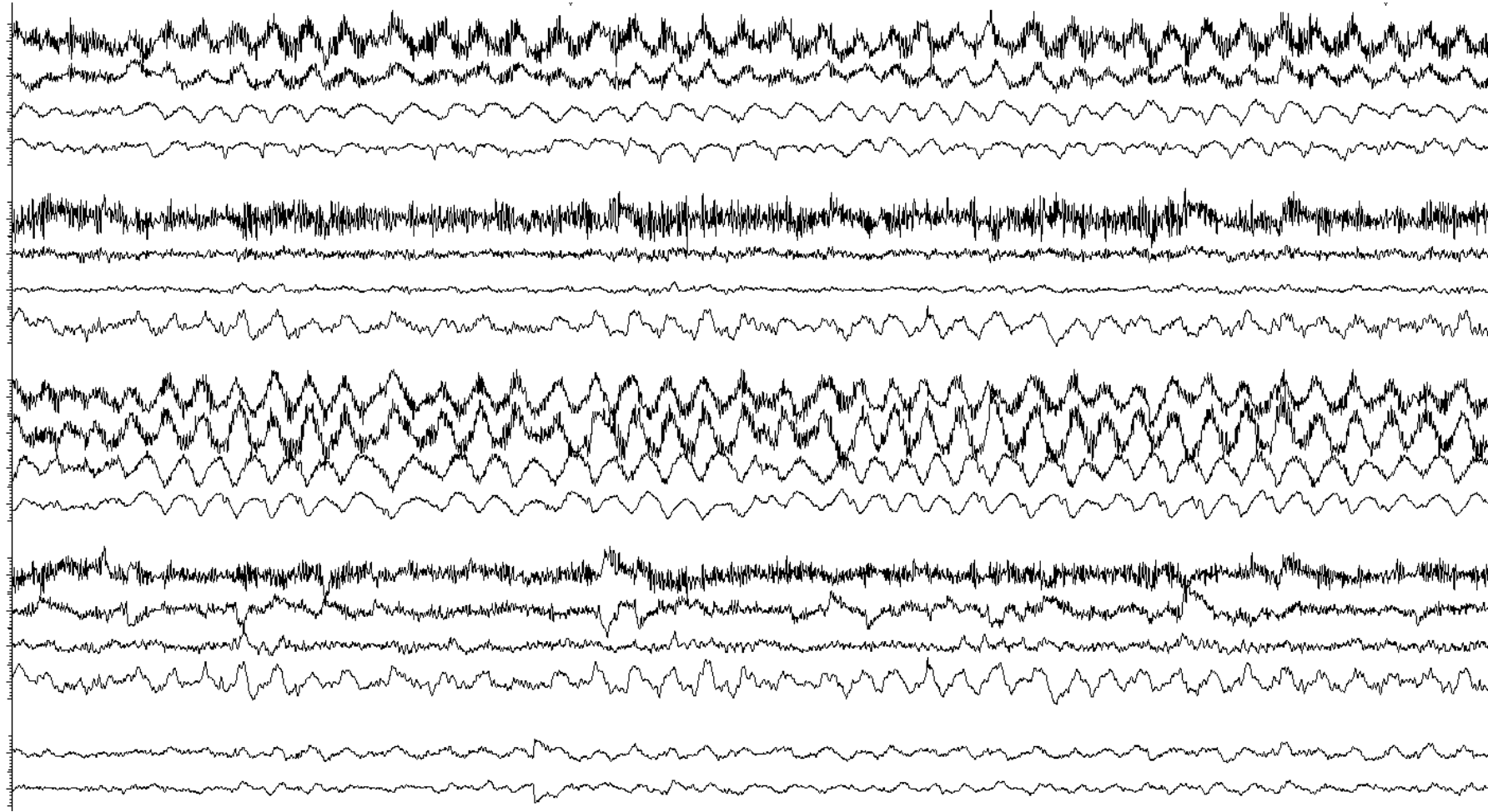
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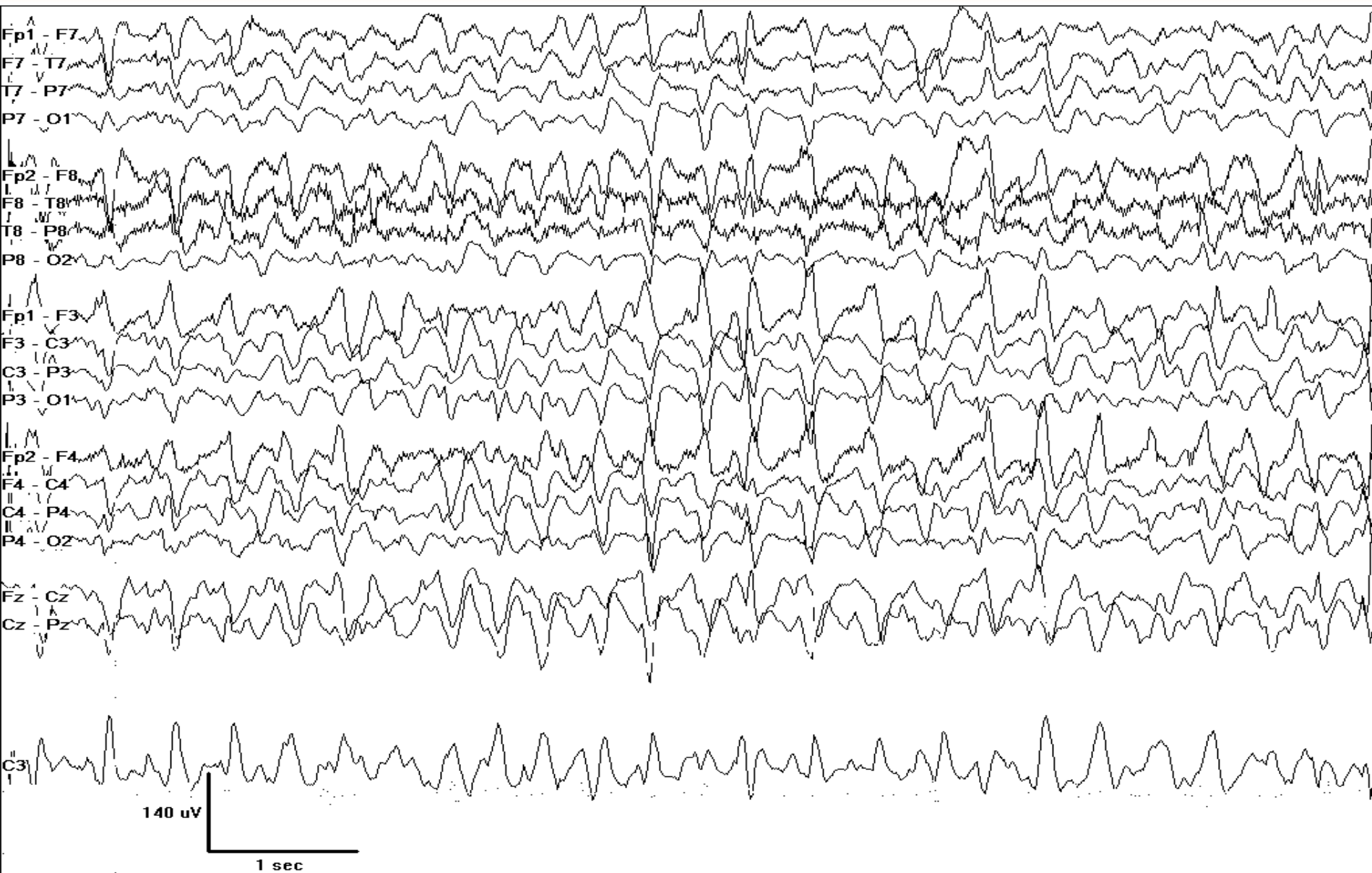
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T8-P8
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Cz-Pz
8.470 $\mu\text{V}/\text{mm}$





A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

Epilepsia, **(*):1–9, 2015

Table 2. Axis I: Classification of status epilepticus (SE)

- (A) *With prominent motor symptoms*
 - A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
 - A.1.a. Generalized convulsive
 - A.1.b. Focal onset evolving into bilateral convulsive SE
 - A.1.c. Unknown whether focal or generalized
 - A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
 - A.2.a. With coma
 - A.2.b. Without coma
 - A.3 Focal motor
 - A.3.a. Repeated focal motor seizures (Jacksonian)
 - A.3.b. Epilepsia partialis continua (EPC)
 - A.3.c. Adversive status
 - A.3.d. Oculoclonic status
 - A.3.e. Ictal paresis (i.e., focal inhibitory SE)
 - A.4 Tonic status
 - A.5 Hyperkinetic SE
- (B) *Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)*
 - B.1 NCSE with coma (including so-called “subtle” SE)
 - B.2 NCSE without coma
 - B.2.a. Generalized
 - B.2.a.a Typical absence status
 - B.2.a.b Atypical absence status
 - B.2.a.c Myoclonic absence status
 - B.2.b. Focal
 - B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
 - B.2.b.b Aphasic status
 - B.2.b.c With impaired consciousness
 - B.2.c Unknown whether focal or generalized
 - B.2.c.a Autonomic SE

Table 3. Currently indeterminate conditions (or “boundary syndromes”)

Epileptic encephalopathies
 Coma with non evolving epileptiform EEG pattern^a
 Behavioral disturbance (e.g., psychosis) in patients with epilepsy
 Acute confusional states, (e.g., delirium) with epileptiform EEG patterns

^aLateralized and generalized periodic discharges with monotonous appearance are not considered as evolving EEG patterns.^{26,27}

Table 4. Etiology of status epilepticus

Known (i.e., symptomatic)
 Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
 Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
 Progressive (e.g., brain tumor, Lafora’s disease and other PME, dementias)
 SE in defined electroclinical syndromes
 Unknown (i.e., cryptogenic)

Convulsive SE

Prominent Motor Features

Generalized

Focal with impaired consciousness

Often excludes EPC

Nonconvulsive SE

Without Prominent Motor Features (Subtle)

With and Without Impairment in Consciousness

(ie aphasia only)

Generalized and Focal

Convulsive SE

Nonconvulsive SE

Ictal-Interictal Continuum

Prominent Motor Features

Without Prominent Motor Features (Subtle)

< 3 hz Non-Evolving, Periodic or Rhythmic Activity

With and Without Impairment in Consciousness

Without Prominent Motor Features

Focal with impaired consciousness

(ie aphasia only)

Often With Impairment of Consciousness

Often excludes EPC

Generalized and Focal

Without Prominent Motor Features

Often With Impairment of Consciousness

Generalized and Focal

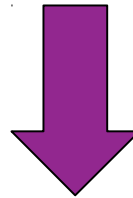


- The longer generalized SE persists, the harder it is to control
- Neuronal damage is primarily caused by continuous excitatory activity, not systemic complications.
- Systemic complications, may exacerbate neuronal damage.

Every seizure counts in terms of making SE, especially convulsive, more difficult to control and for causing neuronal damage.

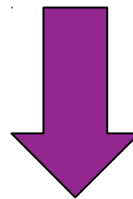
Continuous seizure activity for > 5 min or recurrent episodes without recovery in between episodes

Established Status Epilepticus



Status epilepticus unresponsive to initial standard antiepileptic medications (1st and one 2nd line therapy) ¹ Occurs in 23 - 43% of patients with SE ²

Refractory Status Epilepticus



Seizures continuing despite additional AEDs and/or after the initial continuous infusion of anesthetic agents

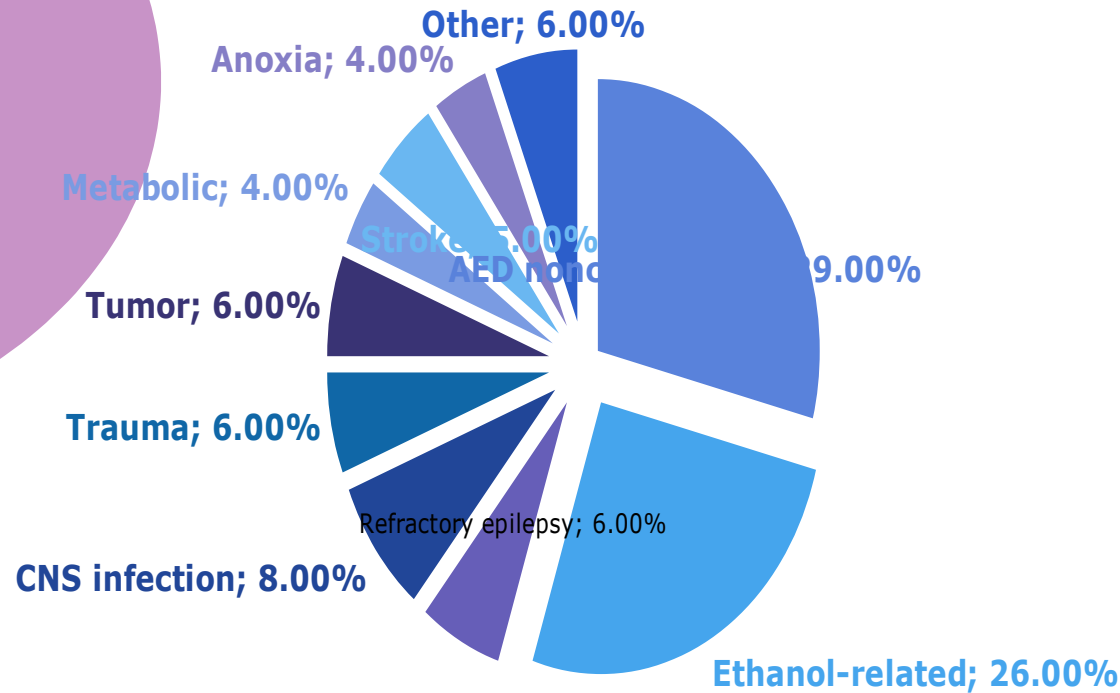
Super-Refractory Status Epilepticus

1. Bleck TP. Refractory status epilepticus. Curr Opin Crit Care 2005; 11:117-120.

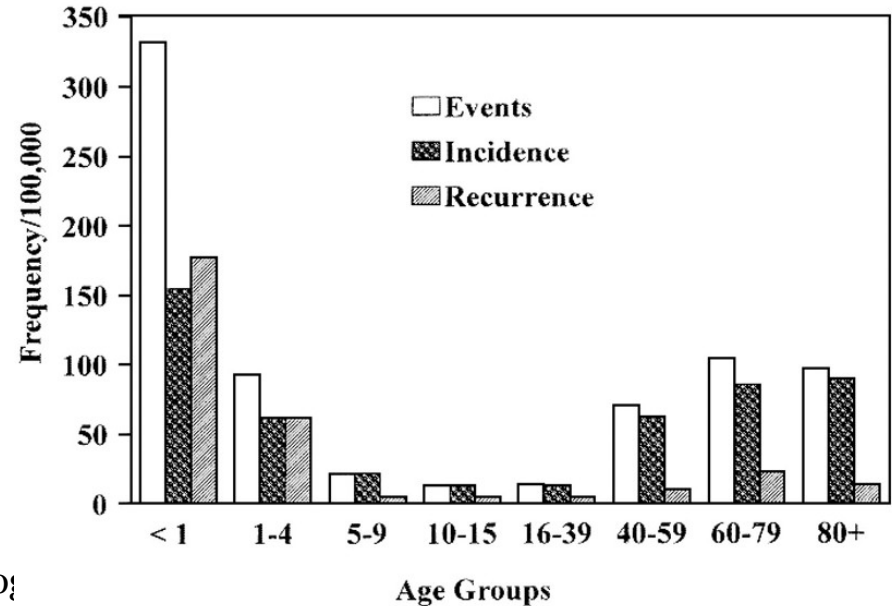
2. Rossetti AO. Management of Refractory Status Epilepticus in Adults. Lancet Neurol. 2011; 10: 922-30

CSE

Prominent Motor Features
Generalized
?Focal with impaired consciousness
Excludes EPC

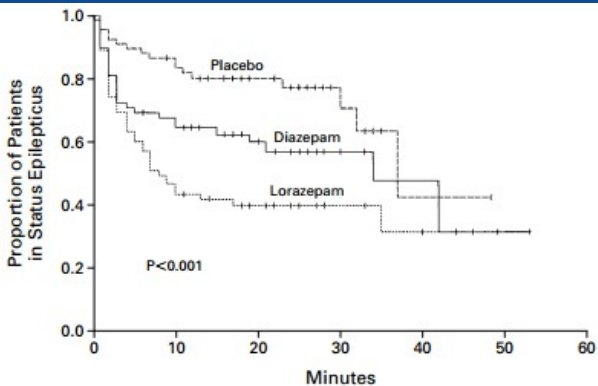


- Incidence 3.6-61/100,000 depending on population
- 3 million of SE/yr
 - 70% GCSE (75% Overt)
- More than half of patients will not have had a prior seizure
- Half of patients will have an acute symptomatic etiology
- SE is the initial presentation of new onset seizure disorder in 1/3 of cases



A COMPARISON OF
TREATMENT

BRIAN K. ALLDREDGE, PHARM.D.,
FAITH ALLEN, M.D., SUEKAY L
JOHN M. NEUH



PLACEBO FOR THE
PILEPTICUS

IGAN D. CORRY, E.M.T.-P., M.A.,
, NELDA O'NEIL, R.N., M.S.N.,
WENSTEIN, M.D.

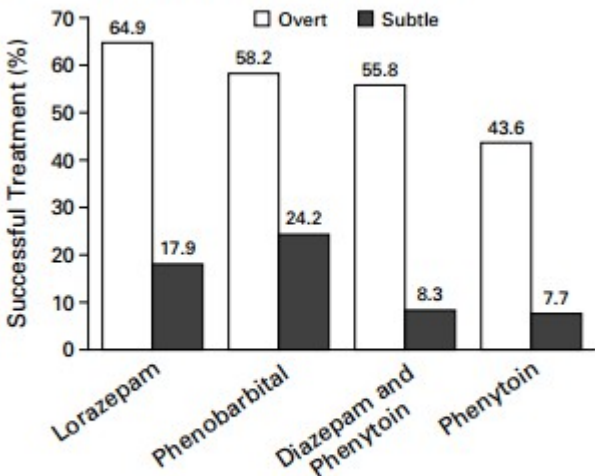
NO. AT RISK

Diazepam	68	41	21	8	2	1
Lorazepam	65	29	15	6	2	0
Placebo	67	53	26	10	1	0

A Patients with Verified Diagnoses

A COMPARISON

DAVID M. TREIMAN, M
CINDY COLLING, R.Ph
VINCENT P. CALABRESE, M.
FOR TH

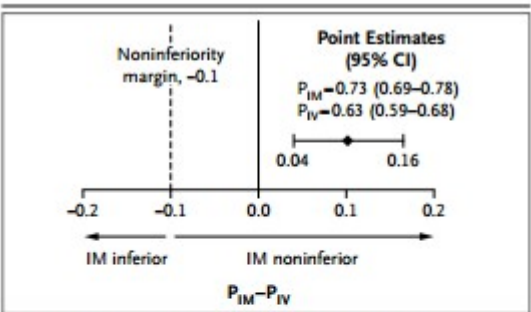


D CONVULSIVE

PH F. COLLINS, Sc.D.,
WARD FAUGHT, M.D.,
LEENAL B. MAMDANI, M.D.,
ROUP*

Intramuscular

Robert Silbergleit, M
Arthur Pancioli, M.D.,



for Prehospital

I.D., Robin Conwit, M.D.,
for the NETT Investigators*

Table 6 Treatment recommendations for SE

Treatment	Class/level of evidence
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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

Urgent treatment

Valproate sodium	Class IIa, level A
Phenytoin/fosphenytoin	Class IIa, level B
Midazolam (continuous infusion)	Class IIb, level B
Phenobarbital	Class IIb, level C
Levetiracetam	Class IIb, level C

Refractory treatment

Midazolam	Class IIa, level B
Propofol	Class IIb, level B
Pentobarbital/thiopental	Class IIb, level B
Valproate sodium	Class IIa, level B
Levetiracetam	Class IIb, level C
Phenytoin/fosphenytoin	Class IIb, level C
Lacosamide	Class IIb, level C
Topiramate	Class IIb, level C
Phenobarbital	Class IIb, level C

My hospital has a status epilepticus management protocol?

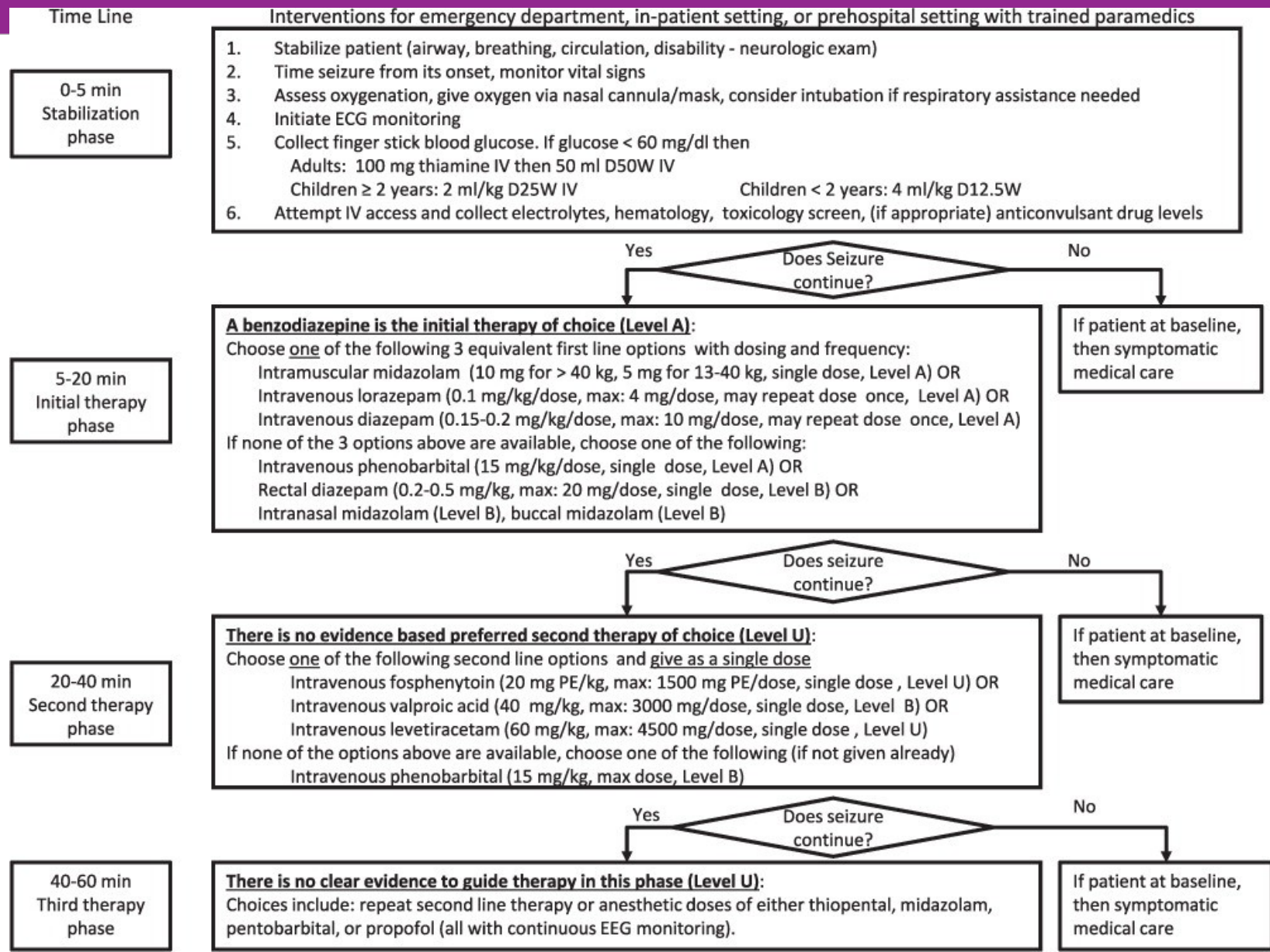
- A. Yes
- B. No
- C. Don't know

We now have high level data to support the use of specific 1st, 2nd and 3rd line agents in the management of status epilepticus?

- D. Yes
- E. No
- F. Don't know

AES Status Epilepticus Treatment Algorithm,

Epil Currents 2016



2016 Treatment Algorithm for Generalized Convulsive Status Epilepticus (SE) in adults and children > 40 kg

Generalized convulsive SE is defined as bilateral convulsive seizure activity for ≥ 5 minutes or ≥ 2 seizures without return to consciousness.

This document is intended to be a general guideline and should not supercede clinical judgment.

Medications

Medical Management/Notes

With IV access established:

Lorazepam: 4 mg IV push over 2 min
If still seizing after 5 min, repeat x 1

If No IV Access:
Diazepam: 20mg using IV soln PR or
Midazolam: 10mg Intranasal/
Buccal/ IM using IV solution (or
commercially available alternative
formulation)

Consult Neurology

- CAB (circulation, airway, breathing)
- Obtain IV access
- Check fingerstick glucose
- Give thiamine 100mg IVx1 prior to dextrose (may administer as vitamin bag)
- Give D50W 50ml IV if low/unknown glucose
- Give pyridoxine 250 mg IV x 1 followed by 100 mg PO daily (unless suspicion of isoniazid toxicity then administer 5 g IV); obtain pyridoxine level (send-out lab)
- Continuous monitoring: O_2 , HR, BP, EKG, $ETCO_2$ (if possible)
- Obtain labs: CBC, BMP, Ca, Mg, P, Troponin, LFTs, ABG, AED levels (if applicable), tox screen (blood/urine), HCG (females)
- Stop lorazepam push at any point if patient stops seizing

If still seizing, continue below

Valproate: 40 mg/kg IV (over 5 – 10 min); max 4000 mg. If still seizing, give additional 20 mg/kg IV (max 2000 mg) over 5 min

OR

Fosphenytoin: 20 mg PE/kg IV at 150 mg/min; max 2000 mg. If still seizing, give additional 5 mg/kg IV (max 500 mg)

OR

Levetiracetam: 60 mg/kg IV (over 15 min); max 4500 mg. If still seizing give an additional 10 – 20 mg/kg IV (max 1500 mg) over 5 min

AND consider continuous anesthetic infusion simultaneously or immediately following AED above, if still seizing AND intubated:

Midazolam*

Load 0.2 mg/kg IV (push over 1 – 2 min); max 20 mg. Repeat 0.2 – 0.4 mg/kg boluses (max 40 mg per bolus) q5min until seizures stop; max total load of 2mg/kg

Infusion: initial 0.1 mg/kg/h; maintenance 0.05 – 2.9 mg/kg/h; titrate to seizure suppression

OR

Propofol* (consider simultaneous benzodiazepine infusion)

Load 1 – 2 mg/kg IV (push over 3 – 5 min); max 200 mg. Repeat q3-5min until seizures stop; max total load of 10mg/kg

Infusion: initial 30 μ g/kg/min; maintenance 30 – 200 μ g/kg/min (1.8 – 12 mg/kg/h); titrate to seizure suppression

- Continuous infusions: before initiating maintenance infusion, repeat boluses until seizures stop; for breakthrough seizures, re-bolus and increase infusion rate
- Prefer short-acting neuromuscular blockade for intubation
- Avoid continuous anesthetic infusions if unable to intubate
- Any medications in this section may be combined

Alternatives:

Phenytoin: 20 mg/kg IV up to 50 mg/min (give at a slower rate of 25 mg/min in elderly patients or with pre-existing cardiovascular conditions); max dose 2000 mg. Infuse through dedicated line with 0.22 micron filter. If still seizing, give additional 5 mg/kg IV (not compatible with dextrose containing fluids)

Phenobarbital: 15 mg/kg IV, may give up to 60 mg/min; max dose 1500 mg. If still seizing, give an additional 5-10 mg/kg.

If other anti-seizure medications are contraindicated, consider:

Lacosamide: 10 mg/kg, max 500 mg IV (over 5 – 10 min). If still seizing, give an additional 5 mg/kg; max 250 mg IV over 5 min.

If still seizing, continue below

Ketamine* (consider simultaneous benzodiazepine infusion)

Load: 1.5 mg/kg IV (push over 3 – 5 min); max 150 mg. Repeat until seizures stop; max total load of 4.5 mg/kg

Infusion: initial 1.2 mg/kg/h; maintenance 0.3 – 7.5 mg/kg/h; titrate to seizure suppression

OR

Pentobarbital*

Load: 5 mg/kg IV at 50 mg/min; max dose 500 mg. Repeat until seizures stop; max total load of 25 mg/kg

Infusion: initial 1 mg/kg/h; maintenance 0.5 – 10 mg/kg/h; titrate to seizure suppression

- If patient is still seizing after 30 min, administer at least 1 continuous anesthetic infusion with boluses
- Begin continuous EEG if patient does not awaken rapidly or if continuous anesthetic infusion is being used
- Treat fever aggressively
- Consider lumbar puncture and/or antibiotics if there is clinical suspicion of infection
- Check autoimmune and paraneoplastic antibodies in serum and CSF, when possible

*Please refer to respective administration guidelines for approved methods of administration. Patients may need to be transferred to higher levels of care to ensure appropriate monitoring.

< 10 min

10 - 30 min

> 30 min

American Epilepsy Soc. Status Epilepticus Guideline www.aesnet.org; Epil Currents 2016

- For initial therapy: IM midaz, IV loraz or IV diaz should be used
- Although IV phenobarb effective, its slower rate of administration positions it as an alternative initial therapy rather than a drug of choice.
 - For pre-hospital or if above 3 benzos not avail, rectal diaz, nasal midaz and buccal midaz are reasonable alternatives (level B)
- For second therapy: No clear choice.
 - Reasonable options include fosphenytoin (level U), VPA (level B) and LEV (level U)
- For third therapy: no clear choice:
 - can repeat second line or use thiopental, midaz, pentobarb or propofol, all w/ continuous EEG monitoring

First 10 min:

With IV access established:

Lorazepam: 4 mg IV push over 2 min

If still seizing after 5 min, repeat x 1

Consult Neurology

If No IV Access:

Diazepam: 20mg using IV soln PR or

Midazolam: 10mg Intranasal/

Buccal/ IM using IV solution (or commercially available alternative formulation)

- CAB (circulation, airway, breathing)
- Obtain IV access
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American Epilepsy Soc. Status Epilepticus Guideline www.aesnet.org; Epil Currents 2016

- For initial therapy: IM midaz, IV loraz or IV diaz should be used (level A, 4 RCTs)
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- For third therapy: no clear choice:
 - can repeat second line or use thiopental, midaz, pentobarb or propofol, all w/ continuous EEG monitoring

Urgent treatment

Valproate sodium

Class IIa, level A

Phenytoin/fosphenytoin

Class IIa, level B

Midazolam (continuous infusion)

Class IIb, level B

Phenobarbital

Class IIb, level C

Levetiracetam

Class IIb, level C

Lacosamide

?

10-30 min

Valproate: 40 mg/kg IV**Fosphenytoin:** 20 mg**Levetiracetam:** 60 mg**AND consider continuing if intubated:****Midazolam ***

Load 0.2 mg/kg IV (push over 1 – 2 min); max 20 mg. Repeat 0.2 – 0.4 mg/kg boluses (max 40 mg per bolus) q5min until seizures stop; max total load of 2mg/kg

Infusion: initial 0.1 mg/kg/h; maintenance 0.05 – 2.9 mg/kg/h; titrate to seizure suppression

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Alternatives:

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Phenobarbital: 15 mg/kg IV, may give up to 60 mg/min; max dose 1500 mg. If still seizing, give an additional 5-10 mg/kg.

If other anti-seizure medications are contraindicated, consider:

Lacosamide: 10 mg/kg, max 500 mg IV (over 5 – 10 min). If still seizing, give an additional 5 mg/kg; max 250 mg IV over 5 min.

00 mg) over 5 min

x 500 mg)

/ (max 1500 mg) over 5 min

bove, if still seizing **AND**

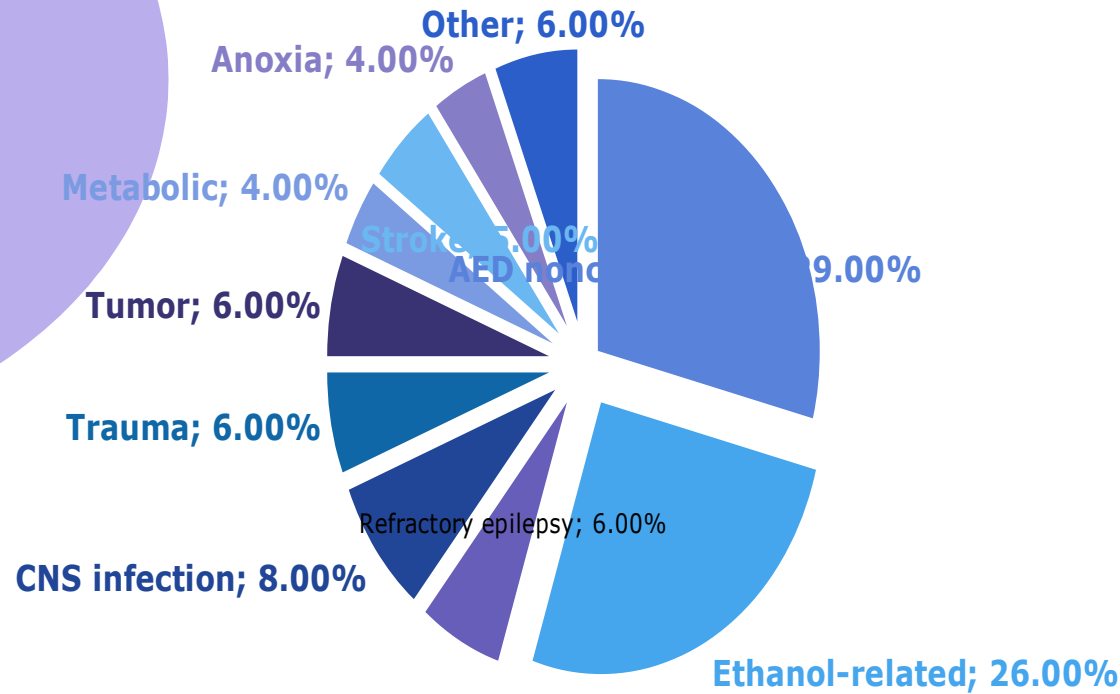
- Continuous infusions: before initiating maintenance infusion, repeat boluses until seizures stop; for breakthrough seizures, re-bolus and increase infusion rate
- Prefer short-acting neuromuscular blockade for intubation
- Avoid continuous anesthetic infusions if unable to intubate
- Any medications in this section may be combined

Established Status Epilepticus Treatment Trial (ESETT)

- Multicenter, randomized, allocation-concealed, Bayesian adaptive, Phase III comparative effectiveness trial.
- The ESE treatment trial is designed to determine the most effective and/or the least effective treatment of ESE among patients older than two years by comparing three arms: fosphenytoin (fPHT) levetiracetam (LVT), and valproic acid (VPA).
- The primary outcome measure is cessation of clinical seizure activity and improving mental status, without serious adverse effects or further intervention at 60 min after administration of study drug.

NCSE

Without Prominent Motor Features (Subtle)
With and Without Impairment in Consciousness (ie
aphasia only)
Generalized and Focal

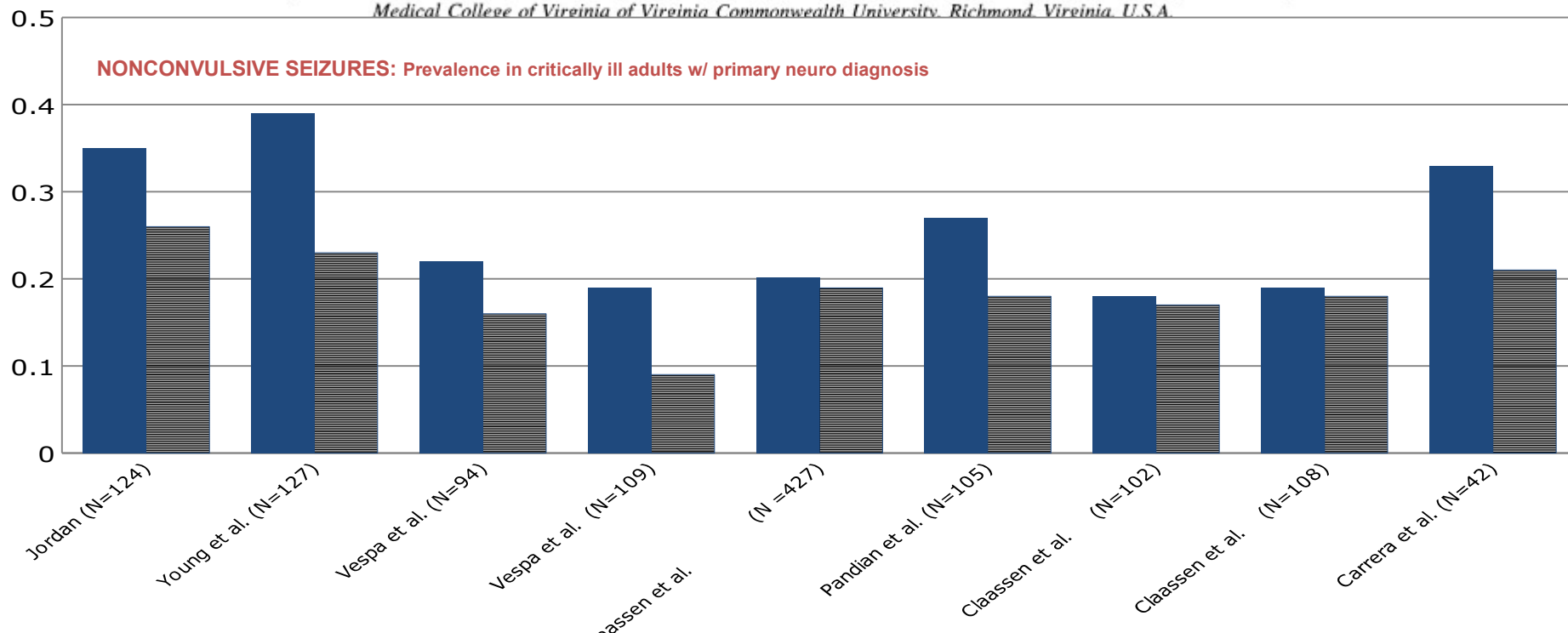


Epilepsia, 39(8):833-840, 1998
Lippincott-Raven Publishers, Philadelphia
© International League Against Epilepsy

Persistent Nonconvulsive Status Epilepticus After the Control of Convulsive Status Epilepticus

*†‡R. J. DeLorenzo, *E. J. Waterhouse, *A. R. Towne, *J. G. Boggs, §D. Ko, *G. A. DeLorenzo,
*A. Brown, and *L. Garnett

*Departments of Neurology, †Pharmacology and Toxicology, ‡Biochemistry and Molecular Biophysics, and §Biostatistics,
Medical College of Virginia of Virginia Commonwealth University, Richmond, Virginia, U.S.A.



- **Husain et al JNNP 2003:** 48 urgent EEGs for possible NCSE; positive in 12; 3 risk factor identified:
 - Severely impaired mental status
 - Oculomotor abnormalities
 - Nystagmus
 - Sustained eye deviation
 - Hippus
 - Remote risk factors for epilepsy
- **Claassen et al Neurology 2004:** 570 consecutive patients undergoing continuous EEG monitoring

Independent predictors of CEEG-documented seizures

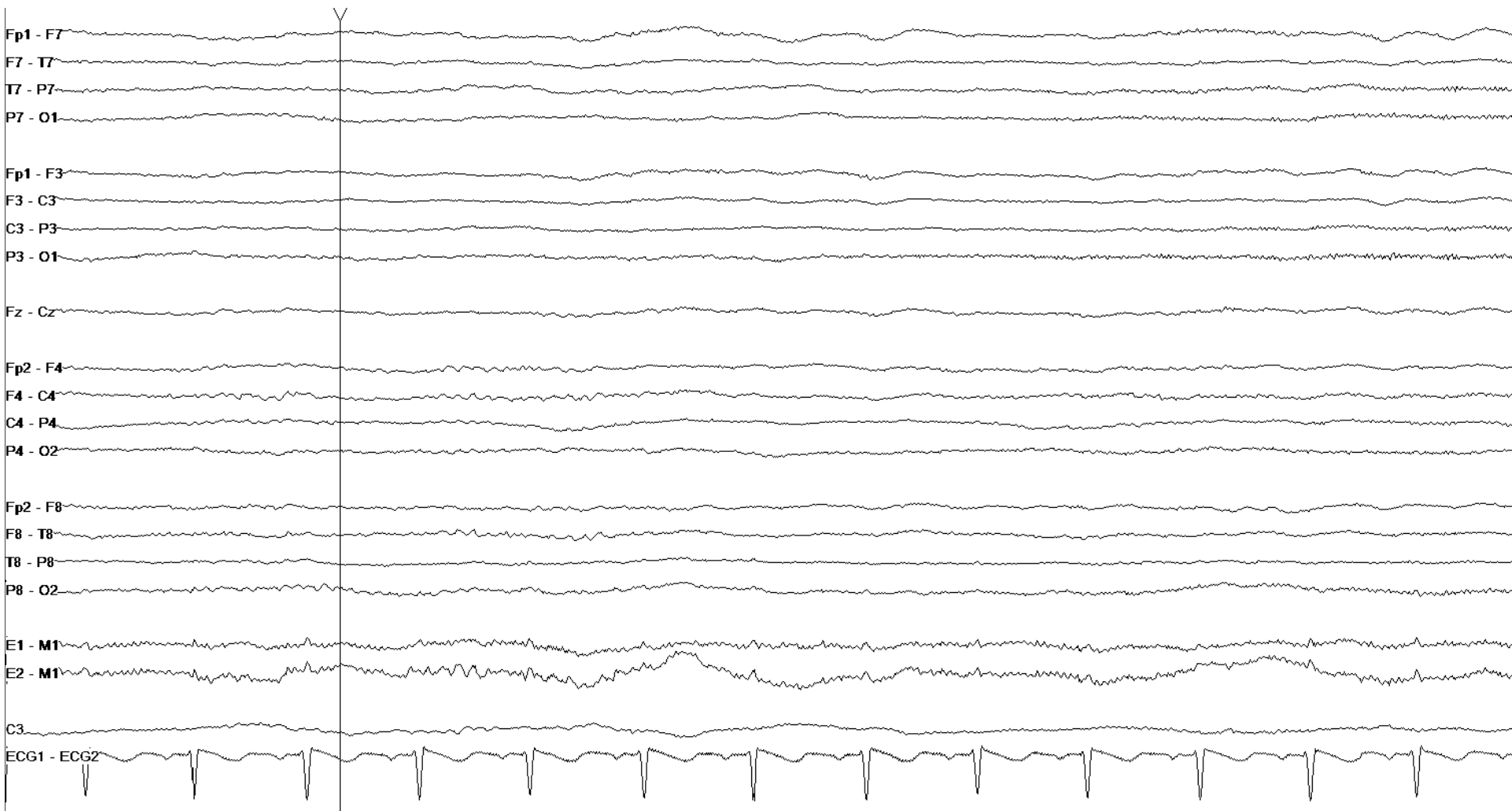
1. **Coma** on neuro exam at start of CEEG
56% of 97 comatose patients vs. 12% of 473 other.
2. **Age** < 18 years
36% of 75 patients <18 y.o. vs. 17% of 495 pts > 18.
3. Past medical history of **epilepsy**
41% of 68 patients w/ PMH epil vs. 16% of 502 w/out.
4. **Convulsive seizures** prior to monitoring
43% of 134 patients with vs. 12% of 436 w/out.
5. Periodic discharges (PLEDs or GPEDs) or Suppression-burst

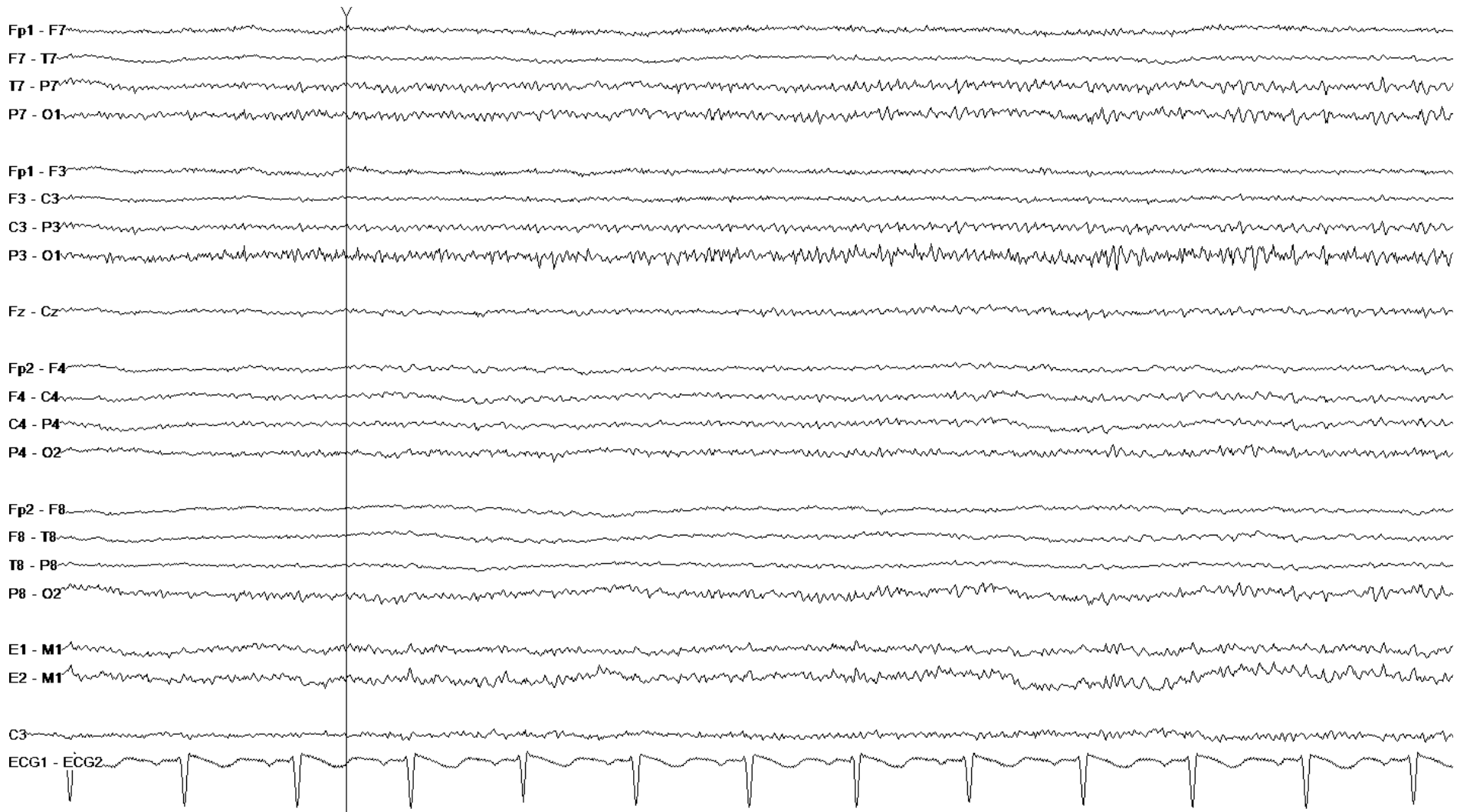
- Focal or generalized spikes, sharp waves, or sharp-and-slow complexes at frequencies >3 Hz
- Focal or generalized spikes, sharp waves, or sharp-and-slow complexes at frequencies <3 Hz or rhythmic activity >0.5 Hz and **ONE** of the following:
 - EEG **AND** clinical improvement after an IV trial of an AED
 - Subtle clinical ictal phenomena during the EEG pattern
 - Typical spatiotemporal evolution, including incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency)
- But for how long?

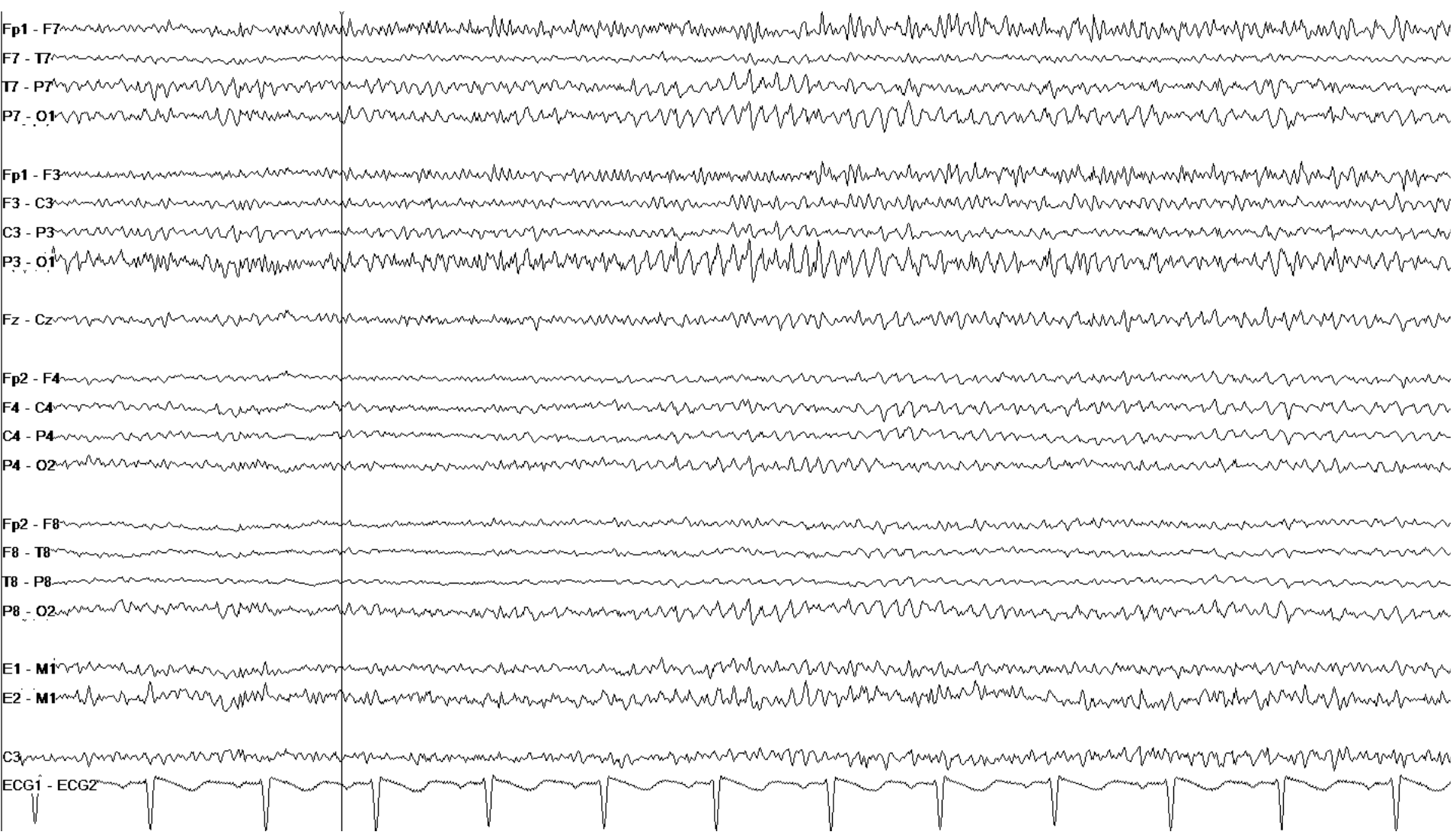
83 year old woman with a PMH of remote ischemic stroke x 2 with aphasia/mild RHP (able to walk with cane), “dementia” and LRE who resents from an OSH where she had been seizing for 5 days despite ginger titration of AEDs and Ativan pushes.

- On arrival, she was not intubated, but was unresponsive with episodes of R gaze preference, R arm extension, lasting about a minute and occurring every 5-6 minutes.
- AEDS: Levetiracetam 1000 mg bid, phenytoin 200 mg bid (had been 300 mg bid), Ativan (received 7-1 mg IVP in the last 24 hours)
- Other meds: Coumadin, metoprolol, risperdone, sertraline, methocarbamol
- PHT level 6









EEG (Summary):

- Frequent seizures arising from the L temporal-occipital region, spreading over the entire L hemisphere and at times to the R hemisphere.
- Occurring 10/hr
- No clear clinical correlate
- Diagnosis: Focal seizures with impaired consciousness

What would you do next?

Yale

Outcome

- Patient was DNR/DNI on arrival - > family changed to DNR
- Loaded with Levetiracetam 2500 mg IV , VPA 30 mg/kg x 2 (level returned at 140) but seizures persisted at 5-6/hr.
- Loaded with Vimpat 400 mg IV after which her seizures stopped.
- She was placed on LVT 1000 mg IV q8, Vimpat 150 mg IV q6, PHT 200 mg q12, VPA 900 mg q12.
- Her admission UA/Uctx was positive for pansensitive Ecoli (> 100k).
- PHT and LVT were weaned off over the subsequent 5 days, her mental status improved, she passed a swallow evaluation and was discharged back to her long-term care nursing facility after a 2 week hospital stay.

Take Home Message

- In the elderly, being aggressive with anesthetics is associated with worse outcome
- If you are going to use non-sedating AEDs, you have to use therapeutic doses
- Have a low threshold to evaluate for occult infection → patients with seizures often meet SIRS criteria
- Engage the family in goals of care discussions early without being overly pessimistic so as not to fall off the self-fulfilling prophecy cliff.

Anti-seizure Medication Trial for the Diagnosis of Non-Convulsive Status Epilepticus

Patients: Rhythmic or periodic focal or generalized epileptiform discharges on EEG with neurological impairment.

Monitoring: EEG, pulse ox, BP, ECG, respiratory rate, with dedicated nurse.

Antiepileptic Drug Trial:

- Sequential small doses of rapidly-acting short-duration benzodiazepine such as midazolam at 1mg/dose, or a non-sedating IV AED. (lev, lacos, fpht/pht, vpa).
- Between doses, repeated clinical and EEG assessment.
- Trial is stopped after any of the following:
 - Persistent resolution of the EEG pattern (and exam repeated)
 - Definite clinical improvement
 - Respiratory depression, hypotension, or other adverse effect
 - A maximum dose is reached (such as 0.2 mg/kg midazolam, though higher may be needed if on chronic benzodiazepines)
- Test is considered positive if there is resolution of the potentially ictal EEG pattern AND either an improvement in the clinical state or the appearance of previously-absent normal EEG patterns (eg. posterior dominant “alpha” rhythm). If EEG improves but patient does not, the result is equivocal (“possible NCSE”)

Do patients wake up after treating NCSE?

If so, when?

- Beth Israel Deaconess, Boston
- Of 68 patients with seizures on EEG in an ICU, excluding post-arrest, 38 (56%) improved in alertness, including 25/52 comatose patients
- Improvement not immediate, but often same day
- 21/38 responders survived vs 1/30 of others
- Didn't use anesthetics

Refractory treatment

Midazolam

Class IIa, level B

Propofol

Class IIb, level B

Pentobarbital/thiopental

Class IIb, level B

Valproate sodium

Class IIa, level B

Levetiracetam

Class IIb, level C

Phenytoin/fosphenytoin

Class IIb, level C

American Epilepsy Soc. Status Epilepticus Guideline www.aesnet.org; Epil Currents 2016

- For initial therapy: IM midaz, IV loraz or IV diaz should be used (level A, 4 RCTs)
 - Although IV phenobarb effective, its slower rate of administration positions it as an alternative initial therapy rather than a drug of choice.
 - For pre-hospital or if above 3 benzos not avail, rectal diaz, nasal midaz and buccal midaz are reasonable alternatives (level B)
- For second therapy: No clear choice.
 - Reasonable options include fosphenytoin (level U), VPA (level B) and LEV (level U)
- For third therapy: no clear choice:
 - can repeat second line or use thiopental, midaz, pentobarb or propofol, all w/ continuous EEG monitoring

> 30 min

Ketamine • (consider simultaneous benzodiazepine infusion)

Load: 1.5 mg/kg IV (push over 3 – 5 min); max 150 mg. Repeat until seizures stop; max total load of 4.5 mg/kg

Infusion: initial 1.2 mg/kg/h; maintenance 0.3 – 7.5 mg/kg/h; titrate to seizure suppression

OR

Pentobarbital•

Load: 5 mg/kg IV at 50 mg/min; max dose 500 mg. Repeat until seizures stop; max total load of 25 mg/kg

Infusion: initial 1 mg/kg/h; maintenance 0.5 – 10 mg/kg/h; titrate to seizure suppression

- If patient is still seizing after 30 min, administer at least 1 continuous anesthetic infusion with boluses
- Begin continuous EEG if patient does not awaken rapidly or if continuous anesthetic infusion is being used
- Treat fever aggressively
- Consider lumbar puncture and/or antibiotics if there is clinical suspicion of infection
- Check autoimmune and paraneoplastic antibodies in serum and CSF, when possible

IIC

< 3 hz Non-Evolving Periodic or Rhythmic Activity

Without Prominent Motor Features

Often With Impairment of Consciousness

Generalized and Focal

Dividing EEG patterns in encephalopathic or comatose patients into a strict dichotomy of "ictal" or "not ictal" is not only extremely difficult, but can be misleading to clinicians and therefore potentially.



The ictal-interictal continuum (IIC)

- Interictal: <1 Hz
- Ictal: clinical correlate; evolving; or >2.5 Hz
- IIC: Typically between 1 and 2.5 Hz, fluctuating, and either rhythmic (RDA), periodic (PDs), or both (PD+R or RDA+S); much less commonly SW (spike-wave or sharp-wave)
- Note that this includes “triphasic waves”
- Might also include frequent nonconvulsive seizures occupying $\sim 50\%$ of a recording

Value of benzo trial for possible NCSE

Hopp JL et al, The Neurologist 2011 (U. Maryland)

- 62 patients with benzo trial for impaired consciousness with epileptiform pattern “potentially consistent with NCSE”
 - Examined immediately and for 1 hour
- 85% of all patients had improvement in EEG
- 22 (35%) had improved consciousness within an hour, and all 22 survived and had good functional outcome
- 40 (65%) did not respond clinically, and only 14 of those 40 (35%) recovered consciousness
- EEG response w/out clinical improvement also correlated w/ modestly higher chance of awakening prior to discharge than having no EEG response, but less strongly, and no correlation with survival

Response rates to anticonvulsant trials in patients with triphasic wave EEG patterns of uncertain significance

O'Rourke D, et al, for the CCEMRC, Neurocrit Care 2015

- 3 institutions (Yale, Columbia, MGH), retrospective, N=64 w/ TW pattern who got benzo trial for possible NCSE
 - 72% had metabolic derangement or infection
 - Excluded postanoxia and those with definite status epilepticus (clinical or on EEG)
- Response: resolution of EEG and either unequivocal improvement in encephalopathy or appearance of previously absent normal EEG patterns
 - Divided into immediate (<2 hours) or delayed
- Benzo trials: 83% loraz, mean dose 2.5 mg; 17% midaz, mean 4 mg
- Non-benzo trials: 69% levetiracetam, 44% pht, 7% lacos, 4% vpa

Response rates to anticonvulsant trials in patients with triphasic wave EEG patterns of uncertain significance

O'Rourke D, Chen, PM, Westover MB, and CCEMRC, Neurocrit Care 2015

- Positive response in 10/53 benzo trials (19%, all immediate) and 19/45 trials with nonsedating AEDs (42%; 7% immed, 20% delayed but definite, 16% delayed and possible).
 - Overall 34% definite positive response and 11% possible
 - No difference in metabolic status in responders and nonresponders
 - No difference in benzo doses between responders and nonresponders
 - Complications of trial: one only: bradycardia, then PEA arrest after load of fospht; recovered.
- Suggests these trials are useful and that many patients with metabolic encephalopathy and “triphasic waves” have an “AED responsive” condition.

Case. #2

- 84 y.o. woman with atrial fibrillation, congestive heart failure, recent right middle cerebral artery stroke for which she underwent mechanical thrombectomy at an outside hospital.
- Hospital course was complicated by septic shock with multiorgan failure re-quiring dialysis, tracheostomy and feeding tube.
- Continuous EEG showed unequivocal nonconvulsive status epilepticus, successfully treated.
- She was discharged to rehab, awake and able to follow simple commands.
- Soon after arriving in rehab, she became less interactive
 - It was felt that AEDs were the culprit so they were decreased.
- When she did not improve, she was transferred to Yale
- Initial EEG: GPDs at 0.5-2.5 Hz, fluctuating



(a)

(b)

(c)

- Lorazepam led to marked improvement in EEG, including improved background and including appearance of sleep spindles; no immediate clinical change
- Gradually awoke over next 48 hours w/ no return of nonconvulsive seizures, interictal-ictal continuum or periodic discharges.
 - No major metabolic or other medical changes over that time period.

“Practical” Treatment Points: IIC

- The dichotomy between ictal and interictal may not exist in many patients.
- The most common continuum patterns are between 1 and 2.5 Hz.
- IV anti-seizure medication trials work.
- Now that we know what to call these patterns, we can study them—need randomized trial.
- Reliable biomarkers of seizure-induced neuronal injury are needed to approach these patients more rationally.

- Many of these cases are often complicated. Intractable conditions can be challenging especially with sparse evidence-based guidance.
- Early treatment is critical, and the identification of an underlying etiology dictates both continued treatment and prognosis.
- Aggressiveness of treatment may be controversial, but timely EEG is useful for diagnosis, management, optimizing treatment response, as well as for determining prognosis.
- Treatment should not be relegated to the nihilistic fate of a self-fulfilling prophecy, especially in younger patients without widespread irreversible brain injury.

Future Directions: SE

- Which AEDs work best?
- What are cost-effective approach for the early identification and treatment of seizures and status epilepticus?
- What are the effects of prolonged EEG monitoring on outcomes?
- What is the effect of early use of anesthetics, their associated complications as well as optimal depth and duration of treatment of RSE and SRSE?
- When should immunotherapy be started?
- Can we develop “dry” electrode EEG devices that can be easily applied without a trained EEG technologist?
- What are the mechanisms of epileptogenesis in this heterogeneous groups of patients with acute symptomatic seizures?

Future Directions: IIC

- Are these patterns surrogate markers for more severely injured brain?
- Do they lead to secondary neuronal injury via excessive metabolic demand, excitotoxicity, or other mechanisms?
- Do they always warrant treatment or at least prophylaxis?
- Should our goal be to decrease burden or make them go away completely?
- How long should we treat?
- Are these patterns associated with the development of epilepsy and long term functional and cognitive outcomes?

- Questions....

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