Status Epilepticus (adult, first 1-6 hrs)

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Protocol: Management of status epilepticus and seizures in hospitalized patients.

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This protocol is for the management of convulsive status epilepticus in adults, and is based on the American Epilepsy Society 2016 Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

For the purposes of this guideline, studies that enrolled subjects having a SEIZURE DURATION OF AT LEAST 5 MINUTES were considered. For details see [https://doi.org/10.5698/1535-7597-16.1.48](https://doi.org/10.5698/1535-7597-16.1.48). See next for commentary on this algorithm, and the next steps beyond this algorithm.

**STABILIZATION PHASE 1-5 MINUTES**

Ensure ABCs, IV access, give O2, EKG monitor

Order CBC, COMP, tox screen, EtOH, beta-HCG, AED levels, troponins. Cool patient if hyperthermic. Head CT. Blood cultures?

Consider your diagnosis.

EEG monitoring may be started in the ER - ask the ER attending for permission. Call the EEG/epilepsy Fellow on-call.

If the cause is unknown, give:

- Thiamine 100 mg
- Folate 1 mg
- 1 amp D50 (only after thiamine and folate)

**INITIAL THERAPY STAGE 5-20MIN; IMPENDING STATUS EPILEPTICUS**

Time equals brain likely also applies to status epilepticus. What are you waiting for?

The initial therapy phase should begin when the seizure duration reaches 5 minutes and should conclude by the 20-minute mark when response to initial therapy should be apparent.
A benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam) is the preferred first AED in managing status epilepticus. For prehospital settings or where the three first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.

Curious as to different medicines in this class? See *Treiman D et al. A comparison of four treatments for generalized convulsive status epilepticus. New Engl J Med 1998; 339; 792-798.* This is an important study that compared the efficacy of lorazepam, diazepam plus phenytoin, phenytoin, and phenobarbital in status epilepticus. There was no difference among the treatment with respect to recurrence or adverse reactions. Lorazepam was recommended as the first line therapy.

Use the medicine immediately available in your patient area.

IV lorazepam and diazepam can be repeated at full doses once (level A, two class I, one class II RCT). Doses listed in the initial therapy phase are those used in class I trials.

- **PREFERRED:** Lorazepam (Ativan) IV stat, 0.1 mg/kg/dose, max. 4mg/dose. Remain at bedside - if continues to convulse then IN 2 MINS, REPEAT DOSE ONCE.
- If only Diazepam (Valium) is available, then use Diazepam IV stat, 0.2 mg/kg/dose, max. 10mg/dose. Remain at bedside - if continues to convulse then IN 2 MINS, REPEAT DOSE ONCE.
- If you cannot get IV access, give Midzolam 10mg IM x1 (use 5mg IM for weight 40kg; midazolam is the only benzodiazepine stable in aqueous solution and is ideal for intramuscular injection).

SECOND THERAPY STAGE 20-40MIN; ESTABLISHED STATUS EPILEPTICUS

Choose ONE of the following. Please send levels (free and total) 1 hr after completing the loading doses.

Curious as to why? The recommendation to switch to a non-benzodiazepine reflects the fact that these medicines are less effective as seizures persist -- for a review, see Chen JW et al, Advances in the pathophysiology of status epilepticus. Acta Neruol Scand Suppl 2007;186:7-

- **PREFERRED:** Fosphenytoin (Cerebyx) IV stat, 20 mg PE/kg (dosed in PE “phenytoin equivalent” units), max. 1500 mg PE. Maximum infusion rate 150 mg PE/min.
  - Requires BP monitoring and EKG monitoring - decr infusion rate if hypotensive, but on balance well tolerated
  - 4A nursing policy requires physician presence during loading with fosphenytoin.
  - If patient has no IV access, give IM. Divide dose into 2 sites for less pain.
  - If 20 mg PE/kg does not stop status, give another 10 mg PE/kg.

- **MYOCLONIC SE OR IGE:** Valproate sodium (Depacon) IV stat, 40 mg/kg over 10-15 minutes, max. 3000mg. Maximum infusion rate of 3 mg/kg/min).
  - excellent option if 1/ hypotensive (VPA does not cause hypotension), or 2/ PHT allergy. But caution in liver patients, or metabolic disease, or women who may be pregnant.
  - Repeat 20 mg/kg bolus over 5 minutes if clinical seizures do not stop.

OTHER OPTIONS:
The usefulness of KEPPRA will be determined (hopefully) by the ongoing Established Status Epilepticus Treatment Trial (ESETT). In the interim, if you elect to use these medicines -

- **PREGNANCY OR SEVERE LIVER DISEASE:** Levetiracetam (Keppra) IV stat, 60 mg/kg, max: 4500mg/dose. Rate 2.5mg/kg/min - maximum infusion rate in literature is 1,000mg in 5 min (Ramael S, Epilepsia, 47 (2006), pp. 1128-1135). MAINTENANCE DOSE [HD3] (but not loading dose) REQUIRES ADJUSTMENT FOR RENAL FUNCTION.

- **LACOSAMIDE (VIMPAT).** IV LCM is increasingly used in the treatment of status epilepticus and initial doses (200–400 mg) are mostly derived from intravenous replacement for oral therapy, but optimal loading dose and target serum levels are unclear. To quickly reach levels within the reference range for LCM of 10–20mg/L, doses of at least 9mg/kg (around 600mg for a 70 kg patient) are required. See Perrenoud M, Epilepsy Res. 2017 Sep;135:38-42. MAINTENANCE DOSE (but not loading dose) REQUIRES ADJUSTMENT FOR RENAL FUNCTION

- **PHENYTOIN (DILANTIN),** IV stat, 20 mg/kg IV load, maximum infusion rate 50 mg/min. Requires BP monitoring and EKG monitoring - ill patients will become hypotensive at this maximal rate, requiring a slower rate. Caution for tissue necrosis (“purple glove” syndrome). 4A nursing policy requires physician presence during loading with phenytoin. If seizures continue, give another 10 mg/kg.

THIRD THERAPY PHASE 40-60MIN; REFRACTORY STATUS EPILEPTICUS

If this doesn't work then INTUBATE and follow the algorithm below. This is by definition refractory SE; 30-60 minutes - discuss this with your attending)

Call anesthesia to intubate the patient, depending on their location.

Call the neurointensivist.

Start looking for an ICU bed (NICU is preferred - or, call the pulmonology fellow to see if you can send the patient to the CCMU until a NICU bed opens up).

FOR ANY OPTIONS IN THIS ALGORITHM BEYOND THIS POINT, intubation and mechanical ventilation with set rate and tidal volume are required. Blood pressure should be monitored frequently - continuous monitoring with an arterial line is preferred. Vasopressors and IV fluids must be immediately available.

You must have EEG monitoring. Call the epilepsy fellow.
The immediate goal is no CLINICAL OR ELECTROGRAPHIC seizures for 24 hrs. Note: There is a lack of evidence regarding whether seizure-suppression or achieving burst-suppression is superior in this setting, and both are considered valid management approaches.

Choose ONE of the following -- starting with either MIDAZOLAM or PROPOFOL, and then Pentobarbital if no effect. Your intensivist may have definite opinions as to the anesthetic they prefer -- and they should be able to cite literature to justify their opinions -- ASK them, politely. For patients requiring sedation for >48 hrs, the combination of propofol and midazolam (to allow lowering the propofol dose) is a reasonable option.

PREFERRED: Midazolam (Versed).

CONTEXT: Most patients who have just been intubated will have received a sizable bolus of midazolam or propofol for anesthesia induction, so the initial bolus can often be deferred.

DOsing:
- Set initial infusion rate at 0.1 mg/kg/h. If continued or recurrent seizures, give a bolus dose of 0.1mg/kg AND revise the infusion rate UP by 0.05 mg/kg/h.
- Midazolam can have fluid volume implications at high doses in a 1 mg/1 mL concentration – U of M pharmacy will actually prepare a 5 mg/mL concentration for you so this should not be an issue for you even at maximal rates.

NOTES: the midazolam doses used in status epilepticus algorithms are significantly higher than critical care guidelines, as well as the maximal dose recommended by U of M guidelines. For your reference –
- In its sedation and analgesia guidelines, the Society of Critical Care Medicine recommends a maximal dose of 0.1 mg/kg/h (so 10 mg/hr for a typical 100kg patient) (Barr et al. Crit Care Med. 2013;41:264; Reade et al. N Engl J Med. 2014;370:444-454).
- The dosing endorsed by pharmacy guidelines at U of M is 1-10 mg/hr, with a maximum allowable dose of 30 mg/hr. See Michigan Medicine Adult Guidelines for Continuous Infusions in ICU, ED and Progressive Care Units.

PREFERRED: Propofol.

CONTEXT:
1. Anesthesiologists typically use an approximately 1 mg/kg bolus in the OR to induce general anesthesia prior to intubation, and this dose frequently causes immediate hypotension – unless you are prepared to immediately correct with pressors, DO NOT DO BOLUS Propofol even though it is the recommended dosing in many status algorithms.
2. Because of its high lipholicity, propofol infusions have onset of action within seconds and bolus dosing in the ICU is typically not necessary.

DOsing
- Titrated to lowest necessary dose, within range of 5 – 80 mcg/kg/min to achieve seizure control or desired level of burst suppression

NOTE: the propofol doses used in status epilepticus algorithms are significantly higher than critical care guidelines, as well as the maximal dose permitted by pharmacy at U of M. For your reference –
- In its sedation and analgesia guidelines, the Society of Critical Care Medicine recommends a maximal dose of 50 mcg/kg/min.
- The maximal dose permitted by Pharmacy protocol is 80 mcg/kg/min. See Michigan Medicine Adult Guidelines for Continuous Infusions in ICU, ED and Progressive Care Units.
- For any patient receiving propofol for more than 24 hrs OR doses >65mcg/kg/min, pharmacy recommends BID monitoring of lactate and CK, as well as QOD monitoring of serum triglyceride levels[HD4]. Try to avoid high-dose infusions greater than 48 hrs. 
- Several algorithms for status epilepticus endorse very high doses of propofol, for example 10mg/kg/hr (167mcg/kg/min; MGH_Status_Protocol_01_09_2015.pdf) and 24 mg/kg/hr (400 mcg/kg/min; Shorvon, Brain 2011;134.2802). Our neurointensivists will generally recommend adding a second agent (midazolam, phenobarbital or ketamine) in super-refractory cases, to avoid these very high Propofol doses.

NOTE: Propofol infusion syndrome is a very rare complication that has been reported in the status literature, likely due to the common practice of using extremely high propofol doses for prolonged periods in these patients. For example, the Mayo case series where 3 of 31 patients on Propofol had cardiac arrest and two died, had received prolonged (median 67 hrs) propofol infusions at doses up to 200 mcg/kg/min, or 2.5 times the U of M maximal dose of 80 mcg/kg/min and 4 times the SCCM-recommended maximal dose (Iyer, Crit Care Med. 37.3024). A strong association has been found for Propofol infusion syndrome and doses greater than 67 mcg/kg/min administered for >48 hrs.

3RD CHOICE: Pentobarbital.

CONTEXT: Invariably STOPs seizures; invariably causes marked hypotension and ileus.

DOSING:
- Load 5 mg/kg at up to 50 mg/min. The goal is to titrate to burst-suppression on EEG using repeated boluses. Repeat 5 mg/kg boluses every 10 minutes until clinical seizures stop.
- Set initial infusion at 1 mg/kg/h and titrate to maintain a burst-suppression pattern on EEG.
- Breakthrough seizures: 5 mg/kg bolus, increase infusion by 0.5–1 mg/kg/h every 12 h
- Continuous infusion rate range 0.5-5 mg/kg/hr (Brophy GM et al. Neurocrit Care. 2012;17(1):3-23)
- As hypotension and respiratory arrest are a given with pentobarbital infusions, appropriate precautions should be taken as prescribed above for midazolam and propofol infusions.
AN ALTERNATIVE, SIMPLIFIED DOSING ALGORITHM

- Load 10 mg/kg over 1 hour.
- If desired level of EEG suppression (typically 1 burst per 10s page) is achieved, continue infusion at 1 mg/kg/hr
- If desired level of EEG suppression is not achieved, load an additional 5 mg/kg over 1 hour, followed by 1 mg/kg/hr infusion
- For breakthrough seizures: 5 mg/kg bolus, increase infusion rate by 0.5–1 mg/kg/h every 12 h as per NCS guidelines

NOTE: If Pentobarbital is not available, may use Phenobarbital 20mg/kg IV at 50-100 mg/min