EM CASES SUMMARY

Episode 133 Emergency Management of Status Epilepticus

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Status Epilepticus Definition

- Continuous seizure lasting > 5 minutes OR
- 2 or more seizures within a 5-minute period without return to neurological baseline in between

Most seizures resolve spontaneously in 1-3 minutes. However, by the time the seizure is identified, physician is notified and attends to the patient, IV access is obtained, drugs are drawn up and given, most actively seizing patients who have not already stopped seizing will be in status epilepticus.

Initial ED management of Status Epilepticus

- Call for help as many steps of the management will occur in parallel.
- ABCDEFG (ABC's and Don't Ever Forget the Glucose) – capillary glucose
- Airway: position in lateral decubitus (when/if possible to minimize aspiration risk) or head up with ongoing suction, nasal trumpets, suction
- Attempt IV access and send for VBG, glucose, electrolytes (Na, Ca, Mg), tox screen, BhCG, CK, Cr, lactate
- Consider crystalloid bolus, draw up push dose pressor for prevention/management of potential hypotension
- IV Lorazepam or IM Midazolam
- If no response to first dose of IV benzodiazepine, start phenytoin/fosphenytoin (avoid in tox), valproate or levetiracetam
- Prepare to intubate via RSI with propofol or "ketofol" and rocuronium (if Sugammadex is available or seizure >20-25 mins) or succinylcholine
- Consider immediate life-threats that require immediate treatment with specific antidotes:
    - Vital sign extremes: hypoxemia (O2), hypertensive encephalopathy (labetolol, nitroprusside) and severe hyperthermia (cooling)
    - Metabolic: hypoglycemia (glucose), hyponatremia (hypertonic saline), hypomagnesemia (Mg), hypocalcemia (Ca)
    - Toxicologic: anticholinergics (HCO3), isoniazid (pyridoxine), lipophilic drug overdose (lipid emulsion) etc.
    - Eclampsia: typically, > 20 weeks of pregnancy and up to 8 weeks postpartum (IV MgSO4 4-6 g over 15-20 min, then infusion 1-2 g/h)

- CT head to rule out space occupying lesion/ICH +/- LP

Note that patients who cease to display tonic clonic seizure may continue to have non-convulsive status epilepticus that can only be detected on EEG.

First line treatment in adult status epilepticus: Benzodiazepines

Choose one of the following first line options (Level A evidence):

1. Lorazepam IV: 4mg q4 minutes, may repeat once (*often underdosed in observational studies)
2. Midazolam IM: 10 mg IM once (*often underdosed in observational studies)

If *neither* of these 2 options are available, choose <u>one</u> of the following:

1. Diazepam IV: 0.15 mg/kg
2. Diazepam PR: 0.2 – 0.5 mg/kg, max 20 mg, single dose
3. Phenobarbital IV: 15 mg/kg, single dose
4. Midazolam IN (0.2mg/kg, max 10mg) or buccal (0.3mg/kg, max 10mg) (Level B evidence)

In patients without established IV access, IM midazolam is preferred. However, the most important determinant of benzodiazepine efficacy in terminating seizures is ***time to administration*** rather than choice of benzodiazepine or the choice of route. The longer a patient seizes, the more refractory to medications they become.

Pitfalls: *In the emergency management of seizures, the biggest pitfalls are underdosing benzodiazepines and dosing too late!*

Should benzodiazepines be administered in seizures < 5 minutes?

Some experts recommend waiting 5 minutes before administering the first anti-seizure medication and giving them slowly over a few minutes because the majority of seizures resolve spontaneously in <5 mins and these medications at therapeutic doses have significant side effects. However, apnea and hypotension are more common with ongoing seizure activity. Aborting the seizure results in less respiratory depression, despite the higher benzodiazepine dose. Our experts recommend *not* waiting 5 minutes before giving the first dose of benzodiazepine, and to give it IV push ideally. In reality, the vast majority of patients who seize in the ED – by the time we draw up the first medication and are actually giving it, several minutes have lapsed and the patient is likely to be in status epilepticus or nearing status epilepticus.

Bottom line: treat seizures **early, IV push** with **adequate doses** of benzodiazepines

Pearl: *Draw up multiple doses of benzodiazepines at the same time at the beginning of the resuscitation to be ready for second dose as needed*

Special Consideration: Alcohol-withdrawal Seizure

In alcohol-withdrawal seizures and status epilepticus, *benzodiazepines* are also considered first line. While phenobarbital has been suggested as an effective first line medication for alcohol withdrawal without seizure, there is no evidence that phenobarbital alone is superior to benzodiazepines for alcohol withdrawal seizures/status epilepticus.

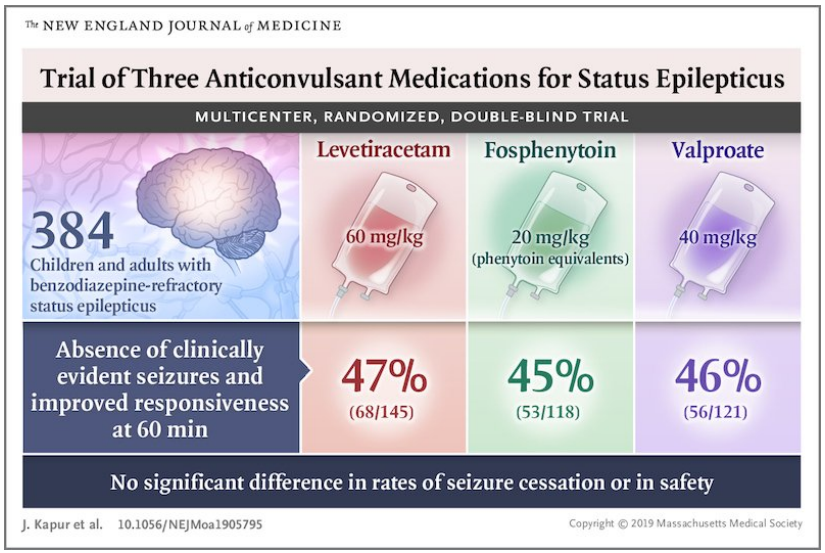
Second line treatment for status epilepticus

If benzodiazepines fail and the patient is still seizing, start second line medications. Status epilepticus can progress into non-convulsive status epilepticus and it can be difficult to diagnose without EEG monitoring. In the ED, observe for a progressive return to baseline within 60 minutes. If observed seizing cesses but there is no return to near-baseline mental status within 60 minutes, there should be concern for non-convulsive status epilepticus. For patients requiring ongoing infusions of sedating medication or are have received a paralytic, non-convulsive status can only be ruled out by EEG. Bottom line is if there are ongoing subtle motor movements or no progression towards baseline mental status, err on the side of caution and continue to treat for status epilepticus until EEG monitoring is available. Choose one of the following equivalent second line options as a ***single dose***:

- Levetiracetam 60 mg/kg IV, max 4500mg
- Fosphenytoin or Phenytoin 20 mg/kg IV, max 1500mg
    - *avoid in toxicologic causes of seizure*
    - *contraindicated in pregnancy*
- Valproate 40 mg/kg IV, max 3000mg

Update 2010: ESETT Trial

In adults and children with persistent benzodiazepine refractory generalized convulsive SE, it was found that there was *no difference* between the use of levetiracetam, fosphenytoin and valproate in seizure cessation and improved alertness by 60 minutes.



Phenytoin vs Fosphenytoin

The efficacy of phenytoin and fosphenytoin for time to seizure cessation are comparable, however there are theoretical reasons why fosphenytoin might be preferred:

Phenytoin	Fosphenytoin
Active drug	Prodrug of phenytoin
Slower rate of infusion (mixed in propylene glycol)	Faster rate of infusion (water soluble)
Can precipitate in IV solutions	Does not precipitate
Can cause cardiac arrhythmias or hypotension	Fewer cardiovascular side effects
Extravasation or *purple glove syndrome* leading to tissue necrosis	Fewer tissue side effects
***Avoid both agents if patient is already on either agent, or suspected toxicological cause of seizure as can cause additional Na blockade effects**	

Phenytoin and fosphenytoin have sodium channel blockade effects, which is similar to the mechanism of action of certain toxidromes such as TCA and cocaine overdose. The additional Na channel blockade of phenytoin/fosphenytoin can result i cardiac dysrhythmias/CV collapse. These drugs should generally be avoided in toxicological causes of seizure for this reason.
If patient has known seizure disorder and is *already* taking phenytoin, our experts recommend choosing a different medication. Drug levels take time to result and if they are already therapeutic on phenytoin, then it is unlikely that loading them with more would be unlikely to be efficacious and likely to increase the incidence of cardiotoxicity.

Pearl: Do not use phenytoin/fosphenytoin in status epilepticus in patients who are known to be taking these medications prior to arrival (increased risk of cardiovascular side effects) or have suspected seizure due to toxicologic cause (increased risk of Na blockade effects leading to cardiovascular collapse)

Use of propofol as second line agent in status epilepticus

There is emerging literature to support the use of propofol as a second line anti-epileptic *in tandem with traditional second line agents,* but controlled data is limited.

The recommended dose is propofol IV bolus 2 mg/kg, followed by 50-80 mcg/kg/min (3-5 mg/kg/hr) infusion.

All second line medications recommended by the guidelines take time to draw up and time to infuse, therefore taking a long time until cessation of seizure (examples are ConSEPT and EcLIPSE trials in children showing 30-45min until cessation of seizure). Propofol is readily available, familiar, can be given quickly, and has a rapid onset of action. In addition, it is a safe option in the suspected toxicological case.
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Refractory Status Epilepticus

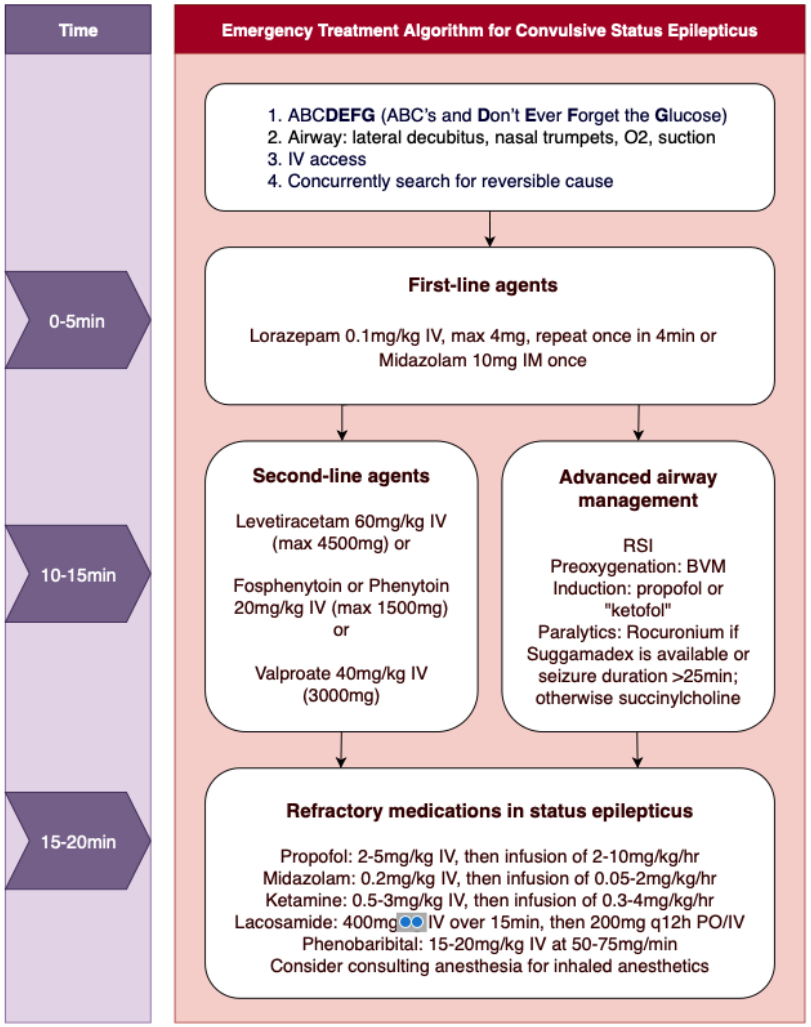
If the patient continues to seize after first and second line treatment, they are in refractory status epilepticus. Therapeutic options include midazolam infusion, ketamine or another second line anti-epileptic medication not already used.

Medication options in refractory status epilepticus

- **Propofol** 2-5 mg/kg IV, then infusion of 50-80 mcg/kg/min (3-5 mg/kg/hr)
- **Midazolam** 0.2 mg/kg IV, then infusion of 0.05-2mg/kg/hr
- **Ketamine** 0.5-3 mg/kg IV, then infusion of 0.3-4mg/kg/hr
- **Lacosamide** 400 mg IV over 15min, then maintenance of 200mg q12h PO/IV
- **Phenobarbital** 15-20mg/kg IV at 50-75mg/min
- Consider consulting anesthesia for **inhaled anesthetics**

The longer convulsive SE continues, the less convulsive it appears clinically, and continuous EEG monitoring should be instituted as soon as feasible.

EM Cases algorithm for ED management of status epilepticus



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Advanced Airway Management in Status Epilepticus (Dr. George Kovacs)

Why intubate?

Predicted clinical course of prolonged seizure with respiratory depression with use of escalating doses of benzodiazepine

When to intubate?

1. If aspirating or apneic
2. If no response to first adequate dose of benzodiazepine

How to intubate?

Rapid Sequence Induction (RSI)

Preoxygenation

Status epilepticus precludes adequate preoxygenation and denitrogenation, and patients are at a high risk of rapid desaturation with high O2 consumption rates. Place nasal trumpets and non-rebreather facemask to provide apneic oxygenation. Consider bagging patient with BVM until laryngoscopy.

Induction agent

Propofol or propofol + ketamine (may have synergistic effect through modulating GABA and NMDA receptors)
Propofol IV 1.5-2 mg/kg
Ketamine IV 1-2 mg/kg
Have on hand rescue vasopressors as needed.

Paralytic: Roc vs Succs

Our experts recommend using a paralytic agent to maximize your chance of first pass success in status epilepticus patients. There is no evidence showing that any particular paralytic improves outcomes in status epilepticus over another. Long-term neuromuscular blockade should be avoided so that clinicians can monitor for ongoing seizure activity and conduct serial neurological exams until EEG monitoring is available. The choice of paralytic agent depends on patient factors, duration of seizure activity and access to the Rocuronium reversal agent, Sugammadex. If there are no clear contraindications for using succinylcholine and the patient has been seizing for <20-25 min, it is reasonable to use succinylcholine given its short duration of action. If Sugammadex is available, then rocuronium can be considered. Suggamadex should only be used in a controlled fashion to reverse the rocuronium after the airway has been secured and the patient has been stabilized. Its purpose in status epilepticus is only to reveal underlying physical seizure activity to aid in titrating sedative infusions, rather than as a tool to be used for a anticipated difficult/challenging airway.

Take home points for emergency management of status epilepticus

- Call for help – many of the initial steps happen in parallel including ABCDEFG (ABC's and Don't Ever Forget the Glucose), IVs, bloodwork, drug preparation, securing the airway
- First line benzodiazepine options: Lorazepam IV (may repeat once) or Midazolam IM (give once)
- If first line benzos not available, you can give: IV Diazepam, Phenobarbital IV, Diazepam PR or Midazolam IN or buccal
- In the emergency management of seizures, the biggest pitfall is underdosing benzodiazepines and dosing too late
- Four *equivalent* second line treatment options: Levetiracetam, Fosphenytoin, Phenytoin or Valproate
- Patients taking second line agents chronically should not receive their IV equivalent in the ED for cessation of status epilepticus
- Do not use phenytoin/fosphenytoin in patients who have suspected seizure due to toxicologic cause (Na blockade effects)
- Valproate is contraindicated in pregnancy
- Consider giving propofol in parallel with second line agents, but controlled data is still limited
- In refractory SE, consider one of the 2nd line agents that has not been used, Propofol, Midazolam, Ketamine, Lacosamide, Phenobarbital or consider consulting anesthesia for inhaled anesthetics
- Rocuronium is the paralytic of choice for seizures >20-25 minutes duration or if Suggamadex is readily available; otherwise, succinylcholine is the paralytic of choice

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