YaleNewHavenHealth

Yale New Haven Health
Department of Pharmacy, Department of Neurology
Treatment Algorithm for Generalized Convulsive Status Epilepticus (SE) in adults
Guideline, YNHHS

Original Date Approved/Date Effective: 08/2012
Date Reviewed/Revised: 11/2016, 09/2020
Approved by: Formulary Integration Committee

Purpose:

This document will serve as a reference to providers who care for patients with active or working diagnosis of status epilepticus.

The goal of therapy is to terminate both clinical and electrical seizure activity in a safe and timely fashion in order to reduce associated mortality and morbidity.

Scope/Epic Order Type (if applicable):

Status epilepticus order set

Patients admitted to the hospital with an active or working diagnosis of status epilepticus

Population: Adults patient

Reference:

1. Glauser T, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsy Curr. 2016 Jan-Feb;16(1):48-61.
2. Grover EH, Nazzal Y, Hirsch LJ. Treatment of convulsive status epilepticus. Curr Treat Options Neurol 2016;18:11.
3. Brophy GM, Bell R, Claassen J, et al: Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. NeuroCrit Care 2012 Apr;17:3-23.
4. Kapur J, Elm J, Chamberlain JM, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl J Med. 2019;381(22):2103-2113.
5. Husain AM, Lee JW, Kolls BJ, et al. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. Ann Neurol. 2018;83(6):1174-1185.
6. Briggs GG, Freeman RK, Towers CV, Forinash AB. Drugs in Pregnancy and Lactation. Lippincott Williams & Wilkins; 2017

YaleNewHavenHealth

Treatment Algorithm for Generalized Convulsive Status Epilepticus (SE) in adults

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 (Must be ordered via NEU IP Status Epilepticus Order Set)

Medical Management/Notes

< 10 min

With IV access established:

Lorazepam: 4 mg IV push over 2 min,
If still seizing after 5 min, repeat x 1
Do not administer IM or SC

Consult Neurology

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

- CAB (circulation, airway, breathing), obtain IV access, check finger stick glucose
- Continuous monitoring: O_2, HR, BP, EKG, $ETCO_2$ (if possible)
- Obtain labs: CBC, BMP, Ca, Mg, P, Troponin, LFTs, ABG, anti-seizure medication levels (if applicable), tox screen (blood/urine), HCG (females)
- Stop lorazepam IV push at any point if patient stops seizing
- Give thiamine 100mg IVx1 prior to dextrose
- Give D50W 50ml IV if low/unknown glucose
- Consider giving 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)

- **For eclampsia (must be ordered via OB IP GBS Prophylaxis, PPROM and Magnesium Sulfate- Focused Order Set)**
- Magnesium sulphate load dose: 4-6 g IV push over 20 min followed by maintenance infusion dose 1-3 g/hr. Serum magnesium threshold level: 4.8 to 8.4 mg/dL. Consider calcium gluconate 1 gram IV push as needed for the management of suspected magnesium toxicity. Caution if history of Myasthenia Gravis

If still seizing, continue below

10 - 30 min

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

OR

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) at 150 mg/min

If still seizing after administering one of the above, either:

Administer a second agent from the above list OR intubate and initiate continuous anesthetic infusion:

Midazolam*
Load dose: 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
Maintenance Infusion Dose: initial 0.1 mg/kg/hr; 0.1– 2.9 mg/kg/hr; titrate to seizure suppression

OR

Propofol* (consider simultaneous benzodiazepine infusion)
Load Dose: 1 – 2 mg/kg IV bolus via infusion pump (intubated patients only) Max dose 200 mg. Repeat q3-5min until seizures stop; max total load of 10 mg/kg.
Maintenance Infusion Dose: initial 30 mcg/kg/min; maintenance 30 – 200 mcg/kg/min ; 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:
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

Brivaracetam: 6 mg/kg IV (over 5 min); max 400 mg. If still seizing, give an additional 200 mg IV over 5 min

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)

If other anti-seizure medications are contraindicated, consider:
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 still seizing, continue below

> 30 min

Ketamine* (recommend simultaneous benzodiazepine infusion)
Load dose: 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
Maintenance Infusion Dose: initial 1.2 mg/kg/hr; maintenance 0.3 – 7.5 mg/kg/hr; titrate to seizure suppression

OR

Pentobarbital*
Load dose: 5 mg/kg IV at 50 mg/min; max dose 500 mg. Repeat until seizures stop; max total load of 25 mg/kg
Maintenance Infusion Dose: initial 1 mg/kg/hr; maintenance 0.5 – 10 mg/kg/hr; 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.*

For non-convulsive status epilepticus, intermittent seizures, or later stages of refractory status epilepticus

Suggested Order of Medication Use

Non-continuous Infusions (usually do not cause respiratory depression, except phenobarbital)	Continuous Infusions (usually cause respiratory depression)	Enteral Medications Per NG/OG (do not cause respiratory depression at recommended doses)
1. Levetiracetam/valproate/fosphenytoin (or phenytoin)/lacosamide/brivaracetam 2. Phenobarbital	1. Midazolam 2. Propofol (no more than 24 – 48 hours at ≥ 80 mcg/kg/min; consider simultaneous benzodiazepine infusion to decrease propofol requirement) 3. Ketamine (recommend coadministration with midazolam) 4. Pentobarbital	1. Perampanel 2. Topiramate/clobazam/pregabalin 3. Oxcarbazepine/carbamazepine/clonazepam 4. Vigabatrin 5. Other enteral anti-seizure medications

Anti-seizure medication	Dosing LD = loading dose MD = maintenance dose	Clinically relevant pharmacokinetic interactions with other anti-seizure medications	Approximate half-life (hr) in non-critically ill	Dose adjustment in renal impairment (maintenance doses) HD = Hemodialysis CRRT = Continuous renal replacement therapy	Dose adjustment in hepatic impairment (maintenance doses)	Comments
Diazepam	**LD**: 0.25 mg/kg IV push over 1 – 2 min (max 10 mg per dose); repeat every 5 min until seizures stop up to 3 doses or 30 mg. **MD**: not applicable.	Longer half-life compared to other benzodiazepines.	40	Not applicable.	Not applicable.	Rapid redistribution. Active metabolite. IV formulation contains propylene glycol. IV solution may be administered rectally if no IV access.
Fosphenytoin	**LD**: 20 mg PE/kg IV (up to 150 mg/min); max 2000 mg. If still seizing, give additional 5 mg/kg IV (max 500 mg). **MD:** Use phenytoin.	See phenytoin. Conversion half-life to phenytoin ~ 15 to 30 minutes. Note: fosphenytoin is dosed in phenytoin equivalents (PE).				May be administered IM if no IV access (up to 99% absorption after IM administration). Compatible in saline, dextrose, and lactated ringers solution. Non-toxic diluent; ↓cutaneous reactions with extravasation. May cause hypotension, arrhythmias. Obtain peak phenytoin level (free and total) 2-3 hours post IV dose or 4 hours post IM dose.
Ketamine	**LD**: 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. **MD**: initial 1.2 mg/kg/h, range 0.3 – 7.5 mg/kg/h; titrate to seizure suppression.		2.5	None.	Consider dose reduction.	NMDA antagonist; provides an infusion with a different mechanism of action (non-GABA). May have sympathomimetic properties, but can also cause hypotension when HR/SBP ≥ 0.9. May ↑ICP (conflicting evidence).
Lacosamide	**LD**: 10 mg/kg IV over 5-10 min (max 500 mg). If still seizing, give an additional 5 mg/kg over 5 min (max 250 mg IV). **MD**: 200 – 600 mg/day divided q12hr – q6hr.		13	Reduce dose in severe renal impairment (CrCl < 30 ml/min); max 300 mg/day. **HD:** 50% removed; lower dose based on CrCl, divide q12hr and add 50% of am dose to pm dose post HD. **CRRT:** lower dose based on CrCl, then increase total daily dose by 50% and divide q8hr.	Consider dose reduction.	May prolong PR interval or induce tachyarrhythmias, including atrial fibrillation. Max IV push dose is 400 mg administered at a rate of 80 mg/min. May obtain lacosamide drug level.
Levetiracetam	**LD**: 60 mg/kg over 15 min (max 4500 mg). Max IV push dose of 1500 mg administered at a rate of 500 mg/min. **MD**: 1500 – 4500 mg/day divided q8hr – q6hr.		6	Reduce dose based on CrCl. **HD:** 50% removed; lower dose based on CrCl, divide q12hr and add 50% of AM dose to PM dose post HD. **CRRT:** lower dose based on CrCl, then increase total daily dose by 50% and divide q6hr.		May cause behavioral disturbances. May obtain levetiracetam **STAT** drug level. No added therapeutic benefit when coadministered with brivaracetam .

Anti-seizure medication	Dosing LD = loading dose MD = maintenance dose	Clinically relevant pharmacokinetic interactions with other anti-seizure medications	Approximate half-life (h) in non-critically ill	Dose adjustment in renal impairment (maintenance doses) HD = Hemodialysis	Dose adjustment in hepatic impairment (maintenance doses)	Comments
Lorazepam	**LD:** 4 mg IVP over 2 mins; repeat every 5 min until seizures stop up to 3 doses or 12 mg. **MD**: not applicable.		12	Not applicable.	Not applicable.	Rapid redistribution. IV formulation contains 80% propylene glycol; may cause metabolic acidosis. Do not administer IM or SC (IM midazolam preferred if IV access not available).
Midazolam	**LD**: 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. **MD**: 0.1 – 2.9 mg/kg/hr; titrate to seizure suppression.		7	Consider dose reduction: risk of active metabolite accumulation.	Consider dose reduction.	Rapid redistribution. Active metabolites. May be administered via alternate routes: 0.2 mg/kg (up to 10 mg) IM, intranasal, or buccal routes; all well absorbed rapidly.
Pentobarbital	**LD**: 5 mg/kg IVP (up to 50 mg/min); max 500 mg. Repeat until seizures stop; max total load of 25 mg/kg. **MD**: 0.5 – 10 mg/kg/hr; titrate to seizure suppression.		22	None.	Consider dose reduction.	Prolonged half-life (up to 50 hours; dose dependent) May cause hypotension, ileus, myocardial suppression, immunosuppression, thrombocytopenia. IV formulation contains 40% propylene glycol; may cause metabolic acidosis.
Phenobarbital	**LD**: 15 mg/kg IV (up to 60 mg/min); max dose 1500 mg. If still seizing, give an additional 5-10 mg/kg. **MD**: 1 – 3 mg/kg/day given q day or divided q12hr or q8hr.	Strong inducer of UGT, CYP 3A4, 2B6, 2C9, 2A6, 1A2. Dose adjustments of anti-seizure medications including phenytoin and valproate might be necessary.	80	Consider dose reduction. **HD**: give full daily dose in evening after hemodialysis.	Consider dose reduction.	Prolonged half-life (up to 140 hours). May cause hypotension. IV formulation contains 70% propylene glycol; may cause metabolic acidosis. May obtain phenobarbital drug level
Phenytoin	**LD**: 20 mg/kg IVP (up to 50 mg/min; 25 mg/min in elderly and patients with pre-existing cardiovascular conditions). **MD**: 200 - 600 mg/day divided q12hr or q8hr.	Induces CYP 1A2, 2B6, 2C, 3A3/4 Generally avoid use with most CYP3A4 substrates. Coadministration with valproate displaces phenytoin from protein binding sites. Induces metabolism of valproate.	15	None.	Consider dose reduction.	May cause rash, fever, hypotension, or arrhythmias. IV formulation contains 40% propylene glycol; may cause metabolic acidosis. Only compatible in saline (unlike fosphenytoin). Incompatibilities include D5W, potassium, insulin, heparin, norepinephrine, cephalosporin, dobutamine. Severe tissue injury may occur with extravasation, including rare purple glove syndrome. Obtain peak phenytoin (free and total) level 2 hours post IV loading dose
Propofol	**LD**:1 – 2 mg/kg IV over 5 min; max 200 mg. Repeat until seizures stop up to total LD of 10 mg/kg. **MD**: 30 – 200 mcg/kg/min (1.8 – 12 mg/kg/hr); titrate to seizure suppression.		0.6 (extended with prolonged use)	None.	None	May cause respiratory depression, hypotension, hypertriglyceridemia, pancreatitis, and propofol infusion syndrome (metabolic acidosis, bradycardia, cardiac arrest, rhabdomyolysis, renal failure). Contraindicated in patients with hypersensitivity to egg or soy products. Monitor pH, bicarbonate, triglycerides, creatine kinase, lipase with prolonged therapy (> 48 hr) or high doses (> 80 mcg/kg/min or 5 mg/kg/hr).
Valproate	**LD**: 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 **MD**: 2000 – 6000 mg divided q8hr-q6hr	Phenytoin and valproate may displace each other from protein binding sites. Valproate markedly inhibits lamotrigine metabolism → ↑↑ lamotrigine levels and risk of side effects including rash.	12	None.	Caution in hepatic impairment.	Highly plasma protein bound (up to 90%). May cause hyperammonemic encephalopathy (treated with L-carnitine supplementation), hepatotoxicity, thrombocytopenia, and platelet dysfunction. Concurrent use with carbapenems (meropenem, doripenem, imipenem, ertapenem) may result in markedly decreased valproic acid plasma concentrations. May obtain valproate total level 2 hours post IV loading dose Highly teratogenic and associated with other adverse fetal effects

YaleNewHavenHealth

Enteral Agents

Anti-seizure medication	Dosing LD = loading dose MD = maintenance dose	Clinically relevant pharmacokinetic interactions with other anti-seizure medications	Half-life (h) in non-critically ill patients	Dose adjustment in renal impairment (maintenance doses) HD: Hemodialysis	Dose adjustment in hepatic impairment (maintenance doses)	Comments
Brivaracetam	**LD: 100 -** 400 mg. **MD:** 50 – 600 mg/day divided q12hr or q8hr.	↑ concentrations of carbamazepine and phenytoin.	9	None.	Consider dose reduction.	May obtain brivaracetam drug level.
Clobazam	**LD**: 20 – 40 mg. **MD**: 20 – 60 mg/day divided q12hr.	Felbamate: ↑plasma concentrations of N-desmethylclobazam.	Clobazam: 16, N-desmethylclobazam: 39	Caution in severe renal impairment (CrCl < 30 ml/min).	Consider dose reduction: undergoes extensive hepatic metabolism.	Decreased sedation compared to other benzodiazepines. May obtain clobazam and active metabolite (N-desmethylclobazam) drug level.
Carbamazepine	**LD:** 400 – 800 mg. **MD:** 400 – 1600 mg/day divided q12hr.	Major CYP3A4 substrate; major CYP2C19/3A4 inducer. Phenytoin and other CYP3A4 inducers ↓↓levels. Valproic acid and other CYP3A4 inhibitors ↑↑ levels.	24 8 (with prolonged use due to auto-induction; 2-4 weeks)	Consider dose reduction in severe renal impairment (CrCl < 10 ml/min): reduce dose by 25%.	Consider dose reduction: undergoes extensive hepatic metabolism.	Strong association between the risk of developing Stevens-Johnson syndrome/TEN and the presence of HLA-B*1502 allele (documented mostly in Asian decent). Dose-dependent hyponatremia; decreased incidence compared to oxcarbazepine. May obtain carbamazepine drug level.
Cannabidiol	**MD:** 2.5 – 20 mg/kg/day divided q12hr.	CYP3A4 and CYP2C19 substrate. Phenytoin and other CYP3A4 inducers ↓↓levels. Valproic acid and other CYP3A4 inhibitors ↑↑ levels.	58	None.	Consider dose reduction.	Concomitant use of higher doses of cannabidiol and valproate increases the risk of transaminase elevations and hepatocellular injury. Consider discontinuation or dose adjustment of cannabidiol and/or valproate if liver enzyme elevations occur. AST and/or ALT >3 times ULN and total bilirubin >2 times ULN, discontinue treatment. Sustained AST and/or ALT >5 times ULN, discontinue treatment
Gabapentin	**LD:** 1200 – 3600 mg. **MD:** 2400 – 4800 mg divided q8hr – q6hr.		6	Reduce dose based on CrCl. **HD**: dose based on CrCl, administer supplemental dose post HD.	None.	Occasional peripheral edema.
Oxcarbazepine	**LD:** 600 – 1200 mg. **MD:** 600 – 2400 mg/day divided q12hr – q6hr.	↑ concentrations of phenobarbital and phenytoin.	5	Consider 50% dose reduction in severe renal impairment. **HD**: IR formulations preferred.	ER formulation not recommended.	Dose-dependent hyponatremia; more common in elderly. May obtain oxcarbazepine drug level
Perampanel	**LD**: 6-12 mg. **MD**: 12 mg/day.		105	Use not recommended in severe renal impairment (CrCl < 30 ml/min).	Consider dose reduction in mild to moderate hepatic impairment. Use not recommended in severe hepatic impairment.	May cause behavioral issues/agitation
Pregabalin	**LD:** 150 – 300 mg. **MD**:150 – 600 mg/day divided q8hr – q6hr.		6	Reduce dose. **HD**: dose based on CrCl, administer supplemental dose post HD.	None	Occasional peripheral edema.
Topiramate	**LD**: 200 – 400 mg. **MD**: 200 – 600 (reports up to 1600) mg/day divided q12hr – q6hr.	Use with zonisamide and other carbonic anhydrase inhibitors may worsen metabolic acidosis.	21	Reduce dose by ~50% **HD**: supplemental dose may be necessary.	Consider dose reduction.	May cause metabolic acidosis; caution with propofol, acetazolamide, zonisamide and metformin. May cause renal stones. May be associated with oligohidrosis, with risk of hyperthermia, mainly in pediatric patients. May obtain topiramate drug level
Vigabatrin	**LD:** 1500 mg. **MD**: 1000 – 3000 mg/day divided q12hr.		10 (but sustained effect for days)	Reduce dose based on CrCl.	None.	Can only be ordered by vigabatrin REMS Program certified prescribers; additional information can be found at www.vigabatrinrems.com. Potential progressive permanent peripheral vision loss after months to years of use; regular ophthalmology examinations recommended with prolonged use. May markedly reduce liver function test (ALT/AST) in patients with documented liver disease. It is not recommended to use plasma liver function test activity as an index of liver cell damage