# Medication Treatment Pathway- Convulsive or Non-Convulsive Status Epilepticus

Applicability- Any adult patient (>40 kg) with:

1. Generalized tonic, clonic, or tonic-clonic seizures, or focal seizures with decreased level of arousal compromising vital functions with at least one of the following:
   a. Witnessed seizures longer than 5 minutes
   b. ≥2 seizures occurring without a return to baseline after 5 minutes
   c. Seizures with unwitnessed onset that are ongoing at the time of provider assessment

| Timing | Management | Supportive Care/Medication Instructions |
|---|---|---|
| **0-5 Minutes** | **IV Lorazepam** – 4 mg initial dose<br>- Repeat after 2-4 minutes (x1) if seizure persists<br>- If no IV access:<br>  ○ **IM Midazolam** – 10 mg<br>  ○ **Intranasal Midazolam** – 10 mg<br>**AND**<br>Order IV Antiepileptic Drug (AED) (See Below) | - Supplemental $O_2$; ABCs; obtain IV Access (if applicable), Obtain Blood Glucose<br>- ECG/Telemetry, Chem 7, Mg, Ca, Phosphorus, CBC, LFTs, AED levels (when applicable), ABG, toxicology screen (urine and blood), hCG (women of reproductive age<br>- Consider thiamine 100 mg IV **then** 50 mL D50 if blood glucose is low or unable to verified |
| | For ongoing seizures including persistent or progressively decreasing level of consciousness, clinical evidence of overt or subtle seizures | |
| **5-15 Minutes** | **IV Fosphenytoin 20 mg PE/kg** and post-dose phenytoin level<br>OR<br>**IV Levetiracetam 60 mg/kg once**, max dose 4500 mg<br>OR<br>**IV Valproic Acid (Depacon®) 40 mg/kg** once<br><br>Medications can be used concurrently if clinically relevant<br>Consider **Lacosamide** 400 mg IV over 5 minutes if strong reason to avoid intubation | **Fosphenytoin**- rate should not exceed 150 mg/minute, may cause hypotension, avoid in liver failure<br>-No maximum dose if weight-based dosing utilized<br><br>**Levetiracetam**- Preferred in pregnancy (or possible pregnancy) and liver failure, few drug-drug interactions, administer over 10 minutes<br><br>**Valproic Acid**- Administer load over 10 minutes, avoid in liver failure<br>-Preferred for myoclonic seizures |
| | For ongoing seizure, intubate and initiate a sedative AED | |
| **15-45 Minutes** | **Always utilize a loading dose with anesthetic AEDs**<br>**Propofol (Available in Pyxis and arrives faster than Midazolam)**-<br>Load- 2 mg/kg propofol followed by 20-100 mcg/kg/min<br><br>**Midazolam (Preferred AED, compounded by pharmacy)**<br>Load- 0.2 mg/kg midazolam followed by 0.05-2 mg/kg/hr<br><br>*Use either non-titratable order targeting seizure cessation or initiate continuous EEG (cEEG) to titrate to burst suppression<br>Order panels in Epic denote status epilepticus orders<br>See page 2 for further information | **Mechanical ventilation required**<br>Consider initiating propofol and ordering midazolam. Transition from propofol to midazolam when medication arrives from pharmacy if no seizure control from propofol is achieved by that time.<br><br>If physician is available at bedside, consider aggressive boluses of midazolam every 5 minutes until seizure control and then initiate continuous infusion<br><br>After 24-48 hours seizure freedom, wean over 8-24 hours |

# Medication Treatment Pathway- Refractory and Super Refractory Status Epilepticus

Adult patients who have recurrence of status epilepticus or disease that is not controlled 24 hours after initiation are considered super refractory. Evidence supporting treatment is limited and should be individualized to the patient.

| Patient arrives to ICU on EEG | Management | Notes |
|---|---|---|
| **Contraindication to intubation?** | **Optimize 2nd line AEDs with addition of:**<br>**Fosphenytoin**<br>**Valproic Acid (VPA)**<br>**Levetiracetam**<br>**Lacosamide**<br>**Phenobarbital** | **Peak drug level attainment (1-4 hours post loading dose):**<br>Phenytoin: 15-20 mcg/mL<br>VPA: 50-100 mcg/mL<br>*Reload phenytoin or VPA if low (see appendix)<br><br>(Fos)phenytoin and VPA interact with one another, avoid combination if possible |
| Seizures continue | | |
| **Intubate and initiate anesthetic antiepileptic drug** | **Continuous infusion (cIV)** see page 1<br>**Never omit initial bolus. Repeat bolus if clinically indicated every 2-5 minutes until seizure cessation**<br>1. **Midazolam**- 0.2 mg/kg bolus followed by 0.05-2 mg/kg/hr<br>2. **Propofol**- 2 mg/kg bolus followed by 20-100 mcg/kg/min<br>Mechanical ventilation and continuous EEG required | **Midazolam**- 1 mg/1mL patients receiving high doses at risk for fluid overload<br>Up titration of midazolam infusion occurs as rapidly as every 15 minutes if burst suppression not achieved<br><br>**Propofol**- doses up to 100 mcg/kg/min have been utilized in literature but increases risk of propofol infusion syndrome<br>Propofol infusion syndrome monitoring: Triglycerides, CPK, ABG, EKG, K |
| Seizures continue | **Optimize maintenance AEDs** | |
| **Change sedative or add additional sedative** | • Switch **propofol** to **midazolam**<br>• Add **ketamine** to **midazolam**<br>• Switch cIV to **pentobarbital**<br><br>**AND**<br>• Adjust maintenance AEDs | **Ketamine**- NMDA antagonist, may provide synergy to GABA agents<br>Utilize system ketamine orderset and select “status epilepticus” indication<br>Bolus- 2 mg/kg, cIV 1-7.5 mg/kg/hr<br><br>**Pentobarbital**- effective agent but last line due to significant ADEs<br>**Always utilize bolus before adding or increasing infusion**<br>Bolus 10 mg/kg, cIV 1-5 mg/kg/hr |
| Seizures continue | **Optimize maintenance AEDs** | |
| **Maximize AEDs and consider alternative therapies** | • Maximize cIV dosing<br>• Add **ketamine** to **pentobarbital**<br>• Add Ketogenic Diet<br>• Autoimmune-based treatments<br>• Adjust maintenance AEDs | Diuresis suggested when multiple cIVs initiated at high doses to avoid fluid overload<br>See appendix for autoimmune-based treatment and ketogenic diet recommendations<br>Place nasogastric/orogastric tube and consider addition of clobazam, topiramate, perampanel (Non-formulary), carbamazepine (drug interactions), pregabalin/gabapentin (low efficacy) |
| Seizures resolve | | |
| **Seizure freedom 24-48 hours** | • Wean cIV medications one at a time over a total period of 8-24 hours based on EEG results.<br>• Consider weaning 10-25% of dose every 3 hours for midazolam, every 6 hours pentobarbital<br>• Longer wean may be required on a patient by patient basis<br>• Slowly remove maintenance AEDS one at a time, if appropriate | Maximize oral AEDs to facilitate weaning<br>**Failure to wean midazolam:** Add clobazam (Onfi®)- 20-40 mg BID or TID<br><br>**Failure to wean Pentobarbital:** Add phenobarbital 10-15 mg/kg once followed by ~2 mg/kg/day in 2 divided doses |

APPENDIX 1- Drug Dosing Information

| Drug | Dosing<br>LD- Loading Dose, MD- Maintenance Dose | Pharmacokinetics | Monitoring/Adverse Drug Events |
|---|---|---|---|
| **Fosphenytoin** | **LD:** 20 mg PE/kg<br>Re-load: 5-10 mg PE/kg based on free or total phenytoin level<br>**MD:** 5 mg PE/kg/day divided in 2-3 doses | IM administration available if needed<br><br>Undergoes zero-order elimination - small dose changes can result in significant serum concentration increase | -Loading dose requires telemetry<br>-Hypotension<br>-Thrombocytopenia (discontinue and initiate alternate AED)<br><br>-Therapeutic range: total phenytoin- 10-20 mcg/mL<br>Free- 1-2 mcg/mL (up to 3 mcg/mL may be effective)<br>-Daily phenytoin levels NOT recommended<br>-Level should verify initial therapeutic range and then monitor if changes in clinical status |
| **Levetiracetam** | **LD:** Initial: 60 mg/kg, single dose not to exceed 4500 mg<br>**MD:** 500-1500 mg every 12 hours | 100% oral bioavailability, use PO formula if GI tract intact<br><br>Renal elimination, decrease maintenance dose in the setting of renal dysfunction<br><br>HD: administer 50% of daily dose after dialysis on dialysis days<br><br>CRRT: Increase daily dose by 50% and divide 4x daily | Agitation |
| **Valproic Acid** | **LD:** 40 mg/kg, maximum 4000 mg dose<br>If still seizing at 15-30 minutes, consider additional 20 mg/kg dose<br>**MD:** 15-30 mg/kg/day divided every 8 hours (IV, oral solution)<br>Daily doses may be converted to once daily dosing if patient able to swallow | Increases concentration of other drugs through hepatic metabolism inhibitions<br><br>Use of meropenem concurrently with valproic acid may significantly lower serum valproic acid level | -Hepatotoxicity<br>-Hyperammonemia (may be treated with l-carnitine)<br>-Thrombocytopenia (discontinue and initiate alternate AED) |
| **Lacosamide** | **LD:** 400 mg over 5 minutes<br>**MD:** 100-200 mg every 12 hours | 100% oral bioavailability, use PO formula if GI tract intact<br><br>Renal elimination, decrease maintenance dose in the setting of renal dysfunction<br><br>HD: administer 50% of daily dose after dialysis on dialysis days | -Possible somnolence<br>-PR prolongation (telemetry recommended if CV comorbidities)<br><br>-Expensive outpatient- verify insurance co-pay prior to discharge |
| **Phenobarbital** | **LD:** 10-15 mg/kg once followed by<br>**MD:** ~2 mg/kg/day in 2 divided doses | 100% oral bioavailability, use PO formula if GI tract intact | -Phenobarbital level is different than pentobarbital level<br>-Therapeutic range- 20-40 mcg/mL |

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| **Topiramate (PO)** | **LD:** 200-400 mg<br>**MD:** 200-400 mg every 12 hours | Oral agent only, requires NG/OG/G-tube access<br><br>Supplemental dose required in HD | -Renal calculi- hydrate patient well<br>-Metabolic acidosis |
| **Clobazam (PO)** | **LD:** 60 mg once has shown safety and efficacy in several case series<br>**MD:** 20-40 mg BID or TID | Caution in decreased renal function (CrCl<30)<br>Caution in hepatic impairment, dose begins at 5 mg daily | -Possibly less sedation compared with other benzodiazepines |
| | | | |
| **Midazolam** | **LD:** 0.2 mg/kg, may repeat every 5 minutes until seizures stop, maximum cumulative loading dose 2 mg/kg<br>**MD:** initiate drip at 0.05 mg/kg/hr, increase as directed up to every 15 minutes to achieve burst suppression | Caution in renal impairment- max dose should NOTnot exceed 1.5 mg/kg/hr<br><br>Evaluate effectiveness around 1 mg/kg/hr. If burst suppression not achieved, consider escalating therapy | -May accumulate when given at a high rate for several days<br><br>-Large fluid load at high rates |
| **Ketamine** | **LD** 2 mg/kg may repeat in 15 minutes if needed to a maximum cumulative dose of 4 mg/kg load<br>**MD:** 0-7.5 mg/kg/hr initiated at 1 mg/kg/hr | | -Monitor cardiovascular vitals- may induce tachyarrhythmia<br>-Large fluid load at high rates |
| **Pentobarbital** | **LD: Never omit bolus dose.** 10 mg/kg once, repeat at 5 mg/kg if no response within 12 hours and increase maintenance infusion<br>**MD:** Initiate AFTER bolus dose at 1 mg/kg/hr. Increase dose every 12 hours up to maximum dose of 5 mg/kg/hr | Induces hepatic enzyme and may decrease serum level of other medications<br><br>Half life ~24 hours, may be in serum several days after discontinuation of infusion | -Hypotension- consider ordering norepinephrine upon initiation<br>-Ileus - Convert all AEDs to IV if ileus occurs<br>-Large fluid load at high rates<br>-Metabolic acidosis develops after long duration of infusion |
| **Propofol** | **LD:** 1 mg/kg, repeat at EACH rate increase<br>**MD:** 20-100 mcg/kg/min, titrate up every 15 minutes if patient not in burst suppression | Minimal drug interactions, rapid elimination<br><br>Provides 1 kcal/mL, adjust nutrition as necessary | -Propofol related infusion syndrome- Rare but serious cardiac instability at high doses (>50 mcg/kg/min) for several days. Monitor EKG, K, CPK, ABG<br>-Monitor triglycerides every 72 hours, hold if >500 |
| | | | |
| **Autoimmune** | For all autoimmune concerns, consider work-up of autoimmune seizure related labs | | |
| **High dose steroids** | 1000 mg methylprednisolone daily for up to 5 days | | -Hyperglycemia<br>-Impaired wound healing, insomnia, psychosis<br>-Schedule dose in the mornings |
| **Plasmapheresis** | Dosing per nephrology, usually 5 sessions every other day | Dose AEDs after plasmapheresis | -Monitor daily calcium, fibrinogen, INR<br>-Dependent on availability of nephrology |
| **IVIG** | 0.4 mg/kg IBW for 5 doses or 1 mg/kg x 2 doses | Plasmapheresis after administration may minimize the effect of IVIG | -Infusion reaction (pre-treated with hydrocortisone, histamine antagonist, acetaminophen)<br>-Use may be limited on current drug shortage and requires pre-approval from pharmacy |