UNIVERSITY of MARYLAND MEDICAL CENTER

Neurocritical Care Unit
Clinical Practice Manual - Clinical Practice Guideline (CPG 003)
Guideline for the Management of Convulsive Status Epilepticus
Revised March 2020

I. Purpose: To provide guidelines for the management of convulsive status epilepticus

II. Scope: Applicable to adult population only.

III. Background

a. **Rationale:** Status epilepticus (SE) requires emergent, targeted treatment to reduce patient morbidity and mortality. Generalized convulsive status epilepticus is a medical emergency requiring rapid diagnosis and treatment. If left untreated, status epilepticus can rapidly become refractory to therapy and is associated with a high rate of morbidity and mortality. It is defined as continuous generalized seizure activity lasting at least 5 minutes or repeated seizures without return to baseline between seizures. It is imperative to initiate therapy early and rapidly control seizures with adequate doses of first line medications to reduce the likelihood of significant brain damage and neuronal injury. The 30 day mortality of patients with convulsive status epilepticus ranges from 19-27% while non-convulsive status epilepticus is 65%. The mortality rate at 3 months for refractory status epilepticus is 39%. (Brophy GM, 2012) The treatment of non-convulsive status epilepticus is equally as urgent as convulsive status epilepticus due to the associated high mortality. This guideline, however, addresses the protocol for convulsive status epilepticus only. Management of non-convulsive status epilepticus may be similar but is not specifically addressed in this guideline. Adverse effects of SE include both indirect systemic problems resulting from the convulsive state such as impaired ventilation, aspiration and metabolic problems and direct neuronal cell injury from excitotoxicity. (Claassen J, 2012) The etiology of SE should be diagnosed and treated as soon as possible. Available evidence suggests that early and aggressive treatment of status epilepticus improves patient outcomes.

b. **Definition:** Status Epilepticus (SE) is defined as 5 min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery to baseline mental status between seizures. Furthermore, SE is classified as generalized convulsive SE, non-convulsive SE or refractory SE. Most clinical and electrographic seizures last less than 5 min and seizures that last longer often do not terminate spontaneously. Permanent neuronal injury and pharmacoresistance may occur before the traditional definition of 30 min of continuous seizure activity as suggested by animal data. (Jensen S, 2006; Chen JWY, 2006)

c. **Generalized Convulsive Status Epilepticus (GCSE):** defined as convulsions associated with rhythmic jerking of the extremities. Characteristic findings include generalized tonic-clonic movements of the extremities, mental status impairment (coma, lethargy, and confusion), pupillary abnormality, and focal neurological deficits in the post-ictal period such as Todd's paralysis which is a temporary neurological deficit lasting hours to days following a seizure.

d. **Non-convulsive Status Epilepticus (NCSE)**: defined as seizures seen on EEG without clinical findings associated with convulsive SE. For purposes of this guideline, we will focus on the acutely ill patient with severe impairment of mental status as this frequently follows uncontrolled GCSE and is often encountered in the ICU. Severe impairment in mental status in the acutely ill patient may be with or without subtle motor movements such as rhythmic muscle twitches or tonic eye deviation also labeled as "subtle status". Symptoms are also highly variable in these patients and include negative symptoms such as aphasia/mutism, amnesia, catatonia, coma, confusion, lethargy, and staring. Positive symptoms include agitation/aggression, automatisms, blinking, crying, delirium, delusions, echolalia, facial twitching, laughter, nausea/vomiting, nystagmus/eye deviation, perseveration, psychosis and tremulousness. Management of this disorder is often similar to GCSE, but is not specifically covered under this guideline.

e. **Refractory Status Epilepticus (RSE):** defined as status epilepticus that does not respond to the standard treatment regimens for status epilepticus are considered to be in refractory status epilepticus. Patients who continue to have either clinical or electrographic seizures after receiving adequate doses of initial benzodiazepine followed by a second acceptable AED is considered to be in RSE.

IV. Expected Outcomes:

a. Rapid termination of clinical and electrical seizure activity.
b. Maintenance of adequate vital signs
c. Diagnosis and immediate treatment of life-threatening underlying cause

V. Responsibility

a. It is the responsibility of all providers to follow these guidelines as appropriate

VI. Procedure

a. Immediate Concerns of Treatment (See Appendix A for Algorithm)

i. ABC's Airway / Oxygenation: Airway maintenance with oral airway and supplemental oxygen. Adequate preparation for possible endotracheal intubation is recommended. If necessary, short-acting paralytic agents can be used to aid in intubation. Paralytics should not be continued after intubation, as they will mask clinically overt signs of seizure activity, with underlying continuation of seizure activity.

ii. Glucose: Hypoglycemia may be a cause of or result of status epilepticus. Check blood glucose immediately in all patients in status epilepticus. If blood glucose is low or not known give D_{50} 50 ml (or D10 250 mL). If concern for Wernicke's encephalopathy exists, give thiamine prior to D50.

iii. Blood Pressure: Cerebral perfusion is compromised by decreased blood pressure. Hypotension often develops after 30-45 minutes of status epilepticus, no matter which agent is used. Fluids and vasopressors may be necessary to maintain adequate blood pressure.

b. Diagnostic work-up and evaluation: The steps in the diagnostic work-up should be completed as soon as possible, simultaneously and in parallel with treatment. Do not delay initiation of therapy to obtain imaging.

i. Obtain laboratory tests.
   1. Finger stick Blood glucose, CBC, CMP, ABG, Calcium (total and ionized), Magnesium, Phosphorous, Troponin
   2. Antiepileptic drug levels (if applicable)
   3. Toxicology screening, urine and blood (as deemed clinically appropriate or feasible)
   4. Based on clinical presentation, consider comprehensive toxicology panel (i.e. isoniazid, tricyclic antidepressants, theophylline, cocaine, sympathomimetics, alcohol, organophosphates and cyclosporine)

ii. Begin continuous monitoring of vital signs. Pulse ox, HR, BP, EKG

iii. Establish IV access

iv. Begin continuous EEG (cEEG) monitoring as soon as possible and within 1 hr of SE onset if ongoing seizures are suspected. The duration of cEEG monitoring should be at least 24 hrs.

v. Obtain CT scan of head to evaluate for structural lesion, once seizures controlled

vi. Consider MRI and LP based on clinical presentation

vii. Obtain 12 lead EKG

VII. Recommended Drug Treatments (See Appendix A and Appendix B for dosing guidelines)

a. Emergent first-line treatment is a benzodiazepine (IV/IM Midazolam, IV Lorazepam, or IV Diazepam) and should be given within the first 5 minutes. Pre-hospital data has demonstrated lower rates of respiratory compromise in patients treated with appropriate doses of benzodiazepines. (Alldredge, 2001)

i. Lorazepam 0.1 mg/kg **IV** (max: 4 mg) given at a rate of 2 mg/min. May repeat in 5-10 minutes.

ii. Midazolam 0.2 mg/kg **IV** (max: 10 mg) given at a rate of 5 mg/min. May repeat in 5-10 minutes.

iii. Midazolam 0.2 mg/kg IM (max: 10 mg). May repeat in 5-10 minutes

iv. Diazepam 0.15-0.2 mg/kg **IV** (max: 10 mg) given at a rate of 5 mg/min. May repeat in 5 minutes.

b. Urgent second-line treatment within 30 minutes, includes Fosphenytoin, Valproate sodium or Levetiracetam. (Kapur J, 2019) Anesthetic doses of Midazolam or Propofol via continuous infusion (CI) can be given simultaneously in patients with a secure airway. (Claassen, 2002; Rossetti, 2011)

i. See Appendix A

c. For refractory SE (seizures persisting for greater than or equal to 30 minutes) not responding to appropriately dosed and titrated midazolam or propofol infusions, consider the initiation of ketamine or pentobarbital infusion.

d. For post-load drug levels, wait at least 2 hours post-infusion for Fosphenytoin and 1 hour post- Phenytoin or Valproate. The therapeutic goal for Phenytoin is free level 2-2.5 mcg/mL and a total level of 15-25 mcg/mL. See appendix B for dosing and monitoring recommendations.

i. In Patients with Serum Albumin < 2.5: Adjusted Total Concentration = Measured Total Concentration / [(0.2 * albumin) + 0.1]

ii. In patients with CrCl < 10 mL/min: Adjusted Total Concentration = Measured Total Concentration / [(0.1 * albumin) + 0.1]

e. The goal of treatment is cessation of electrographic seizures.

f. Maintain electrographic seizure suppression or burst suppression for 24-48 hours, or as clinically indicated, before gradual withdrawal of continuous infusions of AEDs.

g. Wean continuous infusions over 24 hours or longer as clinically indicated:

i. Midazolam – recommend weaning by 0.1-0.2 mg/kg/hr every hour

ii. Propofol – recommend weaning by 5-10 mcg/kg/min every hour

iii. Ketamine – recommend weaning by 0.1-0.25 mg/kg/hr every hour

iv. Pentobarbital – recommend weaning by 0.1-0.25 mg/kg/hr every hour

h. During weaning, there is no agreement on the recommended EEG titration goal (burst suppression vs. seizure control) or duration of continuous intravenous (CIV) AED therapy for patients with RSE. In one case series, EEG burst suppression did not correlate with outcome (Rossetti AO, 2005), whereas in another series, depth of suppression could not be definitively correlated to outcome (Krishnamurthy KB, 1999). Many experts continue CIV AED therapy for 24–48 h of complete seizure control before gradually withdrawing CIV AED therapy, but this is based purely on expert consensus. Breakthrough seizures seen during weaning or after discontinuation of CIV AED typically will require restarting CIV AED and adding additional non-CIV AEDs. Additionally, clinicians should ensure that all doses of non-CIV AEDs are optimized and goal drug levels are achieved. Patients with recurrent refractory SE after initial withdrawal of continuous AED infusions will require a return to prior or higher doses of the continuous AED infusions for an additional period of time with or without addition of another agent. (Fernandez A, 2012). EEG titration goals will be determined by the NCCU team in conjunction with the EEG/Epilepsy service.

i. There is no defined duration or number of trials of electrographic seizure control for which care is considered futile.

j. Following resolution of RSE, maintenance AED should be given in sufficient doses to maintain therapeutic levels during and after weaning of the continuous infusion.

k. Maintain normothermia.

l. Consider hypothermia

VIII. Procedure for patients being transferred from outside hospital

a. Perform medication reconciliation to include how many doses of AEDs and times of administration.

b. Obtain appropriate drug levels STAT. Free or total phenytoin or valproate levels can be ordered. Total phenytoin and valproate levels are typically reported more rapidly and may be more useful in acute situations. Levetiracetam, Lacosamide and Free Valproate levels are send out labs and will take 3-5 days to report. Free phenytoin levels are batched and processed twice daily at UMMC. If ordering a total phenytoin level, consider also ordering a serum albumin and serum creatinine in order to calculate adjusted total phenytoin level, as stated above in Section VII, d, i-ii.

c. Do NOT load and re-dose with phenytoin / fosphenytoin prior to completion of medication reconciliation and obtaining phenytoin level.

IX. Special Considerations in Pregnancy

a. Pregnant patients presenting with status epilepticus should be treated as any other patient

b. Consult OB/GYN and Epilepsy to individualize treatment

X. Nursing Assessment and Documentation

a. Refer to UMMC Clinical Practice Manual SPP-003 for policy on care of patients with seizures
b. Remain with the patient during the seizure
c. Maintain a patent airway and administer O2
d. Notify provider of seizure as soon as possible
e. Document seizure activity in the progress note / critical care flow sheet / seizure flow sheet.
f. Document all seizure activity on the cEEG monitor using the push button and text features.
g. Educate patient/family about seizures, treatment, and plan of care.
h. Document patient/family education in the plan of care and patient/family education forms.

XI. Treatment Pearls

a. Begin continuous EEG monitoring as soon as possible if patient does not awaken rapidly and if concern for seizure/SE remains. Begin cEEG ideally within 45 minutes of initial assessment of patient in SE.
b. If on continuous IV treatment, once seizures controlled (goals to be determined as in VII above) continue infusion for 24-48 hours. Wean over 24 hours.
c. Obtain CT scan of the head to look for structural lesion once seizures controlled
d. Consider MRI and/or PET / SPECT based on clinical presentation, especially to clarify highly epileptiform inter-ictal patterns
e. Consider LP based on clinical presentation
f. Consider paraneoplastic and/or autoimmune workup as etiology of seizures
g. Maintain normothermia
h. Consider hypothermia, immunomodulation (steroids, intravenous immune globulin, therapeutic plasma exchange), ketogenic diet and electroconvulsive therapy for refractory patients
i. Midazolam can be used as an induction agent when intubating patients with status epilepticus

Appendix A: Generalized Convulsive Status Epilepticus Adult Treatment Algorithm

Initial treatment must address suspected underlying cause since outcome has always been shown to be more dependent on the underlying etiology.

Status Epilepticus:

5 minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery (return to baseline) between seizures

Should be classified as either convulsive (convulsions associated with rhythmic jerking of the extremities) or non-convulsive (seizure activity seen on EEG without the clinical findings associated with convulsive SE)

EMERGENT TREATMENT Within 5 Minutes - First Line Antiepileptic Drugs (AEDs) 1. Lorazepam 0.1 mg/kg actual body weight **IV** (max: 4 mg) given at a rate of 2 mg/min. May repeat in 5-10 minutes 2. Midazolam 0.2 mg/kg actual body weight **IV** (max: 10 mg) given at a rate of 5 mg/min. May repeat in 5-10 minutes 3. Diazepam 0.15-0.2 mg/kg actual body weight **IV** (max: 10 mg) given at a rate of 5 mg/min. May repeat in 5 minutes. If no IV access available a. Midazolam 0.2 mg/kg actual body weight IM (max: 10 mg) b. Diazepam 0.2-0.5 mg/kg actual body weight (max: 20 mg) PR using IV Diazepam product Midazolam 10 mg Intranasal, Buccal, Intraosseous using IV Midazolam product	**EMERGENT TREATMENTS Within 1st 5 Minutes** 1. ABC's; Blood Glucose 2. Begin continuous monitoring of vital signs: Pulse Ox, HR, BP, EKG 3. Establish IV Access 4. Blood Draw: CBC, CMP, ABG, Ca, Mg, Phos, Troponin, AED Levels, Tox Screen 5. Give 50 mL D50 IV unless blood glucose known and not hypoglycemic (BG < 70)
URGENT TREATMENT Within 30 Minutes - Second Line Antiepileptic Drugs (AEDs) **IV/PO Boluses** 1a. **Fosphenytoin Loading Dose** 20 mg/kg actual body weight (max 2000 mg) **IV** (Fosphenytoin is preferred over Phenytoin based on tolerability) a. Phenytoin Max Rate: 50 mg/min (nonformulary at UMMC, use IV fosphenytoin instead) b. Fosphenytoin Max Rate: 150 mg/min c. May give an additional 5-10 mg/kg of either agent 10 minutes later if ineffective 1b. **Valproate sodium Loading Dose** 40 mg/kg actual body weight (max 3000 mg) **IV** given over 10 minutes (or 3-6 mg/kg/min) 1c. **Levetiracetam Loading Dose** 60 mg/kg actual body weight (max 4500 mg) **IV** given over 15 minutes or at a rate of 2-5 mg/kg/min 2a. **Phenobarbital Loading Dose** 20 mg/kg actual body weight (max generally 2000 mg) **IV** given at a rate up to 50-100 mg/min. a. May give an additional 5-10 mg/kg 10 minutes later if ineffective 2b. **Lacosamide Loading Dose** 400 mg **IV** given at a rate of 200 mg / 15 minutes a. Efficacy in status epilepticus remains to be established (Santamarina 2013) **IV Continuous Infusions – patient must be intubated** 1a. **Midazolam** 0.2 mg/kg actual body weight **IV** bolus at a rate of 2 mg/min, followed by a continuous infusion of 0.2-2.9 mg/kg/hr. Typical starting dose 0.2 mg/kg/kr. a. May repeat 0.2-0.4 mg/kg boluses Q5 minutes until seizures controlled 1b. **Propofol** 1-2 mg/kg actual body weight **IV** bolus over 3-5 minutes up to a max loading dose of 10 mg/kg then initiate an infusion at 30 mcg/kg/min	**URGENT TREATMENTS Within 30 Minutes** 1. Consider Intubation: Rapid sequence intubation using short-acting paralytic (succinylcholine) and avoiding etomidate (Voss LJ, 2008) 2. If DNI, omit Midazolam and Propofol infusions 3. Fosphenytoin / Phenytoin / Valproate sodium should be given at the same time as midazolam and/or propofol 4. If no IV access, Fosphenytoin can be given IM at a dose of 10-20 mg/kg
Refractory Status Epilepticus - If Seizures Persist ≥ 30 Minutes Patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable AED *Patients should be intubated and placed on continuous EEG monitoring before initiating the following agents:* 1a. **Midazolam** 0.2 mg/kg actual body weight **IV** bolus at a rate of 2 mg/min, followed by a continuous infusion of 0.2-2.9 mg/kg/hr. Typical starting dose 0.2 mg/kg/hr. a. May repeat 0.2-0.4 mg/kg boluses Q5 minutes until seizures controlled up to a max of 2 mg/kg. b. Breakthrough: Bolus 0.2 mg/kg and increase the rate by 0.2 mg/kg/hr every 1-2 hours if seizures persist 1b. **Propofol** 1-2 mg/kg actual body weight **IV** bolus over 3-5 minutes repeating every 3-5 minutes up to a max loading dose of 10 mg/kg until seizures stop, followed by a continuous infusion at 30 mcg/kg/min. a. Continuous infusion: 20-200 mcg/kg/min. b. Breakthrough: increase infusion rate by 5-10 mcg/kg/min every 5 minutes or give 1 mg/kg bolus plus infusion titration. 2. **Ketamine** (Kramer AH, 2012) 1.5 mg/kg actual body weight **IV** bolus over 3 minutes given every 3-5 minutes until seizures stop up to a max loading dose of 4.5 mg/kg, followed by a continuous infusion of 0.3-7.5 mg/kg/hr. Typical starting dose is 1.2 mg/kg/hr. a. Breakthrough: give a 1.5 mg/kg actual body weight **IV** bolus and increase rate by 0.5 mg/kg/hr 3. **Pentobarbital** 5-15 mg/kg actual body weight (max 1000 mg) **IV** bolus at a rate of ≤ 50 mg/min followed by a continuous infusion of 0.5-5 mg/kg/hr using actual body weight a. Breakthrough: 5 mg/kg actual body weight **IV** bolus (max 1000 mg) and increase rate by 0.5-1 mg/kg/hr every 12 hours using actual body weight 4. **Topiramate** 200-400 mg **NG/PO** * Efficacy in refractory status epilepticus remains to be established. Consider in consultation with NCCU / EEG / Epilepsy service.	**Refractory Status Epilepticus If Seizures Persist ≥ 30 Minutes** 1. Should be on at least one continuous IV infusion with boluses

Appendix B: Antiepileptic Drug Dosing and Properties

Medication	Initial, Loading and Maintenance Dosing	Mechanism of Action	Method of Inactivation	Half-Life (hr)	Protein Binding	Drug Interaction	Targeted Drug Levels	Dose Adjustments	Side Effects / Monitoring / Nursing Considerations
Diazepam (Valium)	IV Load: 0.15-0.2 mg/kg Max: 10 mg / dose Max Rate: 5 mg/min May repeat Dose in 5 minutes. Max: 10 mg / dose PR: 0.2-0.5 mg/kg Max: 20 mg Use actual body weight	Benzodiazepine Enhances the inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride ions.	Hepatic Metabolism Renal excretion	15-100	95-98%	Major Substrate: CYP 2C19, 3A4 Metabolism induced by: Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin		Renal: None Dialysis: None Hepatic: Consider dose reduction in cirrhosis	• Hypotension • Respiratory depression • Short duration of effect for initial doses, may accumulate with repeated dosing • IV contains propylene glycol
Fosphenytoin (Cerebyx)	IV Load: 20 mg PE/kg Max Load: 2000 mg Max Rate: 150 mg/min May repeat dose in 10 minutes: 5-10 mg/kg Maintenance: 5 mg/kg/day in 2-3 divided doses Usually 100 mg IV TID Use actual body weight	Enhances sodium efflux from neurons of the motor cortex, stabilizing the threshold against excitability	Hepatic Metabolism	10-15 (IV)	90%	Strong Inducer of: CYP 1A2, 2B6, 2C, 3A3, 3A4, 3A5, 3A6, 3A7 Metabolism induced by: Carbamazepine, Induces Metabolism of: Carbamazepine, Serum Concentration reduced by: Phenobarbital	PHT Levels Total: 15-25 mcg/mL Free: 1.5-2.5 mcg/mL Monitor free level when on VPA, BZD, other highly protein bound drugs, low albumin or critically ill	Renal: None HD: None Hepatic: Consider dose reduction	• Hypotension • Arrhythmia • Compatible in NS, D5, LR
Ketamine (Ketalar)	IV Load: 1.5 mg/kg given over 3 minutes every 3-5 min until seizures stop up to max of 4.5 mg/kg Initial IV Infusion: 1.2 mg/kg/hr Bolus 1.5 mg/kg and increase rate by 0.5 mg/kg/hr until seizure control IV Maintenance: 0.3-7.5 mg/kg/hr Typical Starting Dose: 1.2 mg/kg/hr Use actual body weight	Noncompetitive NMDA receptor antagonist, blocks glutamate, reduces polysynaptic spinal reflexes,	Hepatic Metabolism	2.5	45%	Major Substrate of: CYP 2B6, 2C9, 3A4 Metabolism induced by: Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin		Renal: None Dialysis: Unclear Hepatic: Consider dose reduction	• Caution in patients with cardiac disease • Hypertension • Increased ICP • Consider combining with benzodiazepine to decrease requirement

Medication	Initial, Loading and Maintenance Dosing	Mechanism of Action	Method of Inactivation	Half-Life (hr)	Protein Binding	Drug Interaction	Targeted Drug Levels	Dose Adjustments	• Side Effects / Monitoring / Nursing Considerations
Lacosamide (Vimpat)	IV Load: 400 mg Maintenance: 100-200 mg IV BID Doses ≤ 400 mg can be given IV push. - Give 100 mg over 2 minutes - Give 200 mg over 3 minutes - Give 400 mg over 5 minutes. Doses > 400 mg should be given as IV piggyback	Stabilizes hyperexcitable neuronal membranes and inhibits repetitive neuronal firing by enhancing the slow inactivation of sodium channels	Hepatic: 60% Renal: 40%	13	< 15%	Substrate of: CYP 3A4, 2C9, 2C19 Metabolism induced by: Carbamazepine Carbamazepine and Lacosamide combination may increase AV blocking effect of Lacosamide. Serum concentrations reduced by 15-20% by: Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin,	5-10 mg/L	Renal: Consider dose reduction CrCl < 30 max dose 300 mg / day HD: 50% removed Add 50% of AM dose to PM dose post-dialysis CRRT: Consider increasing total daily dose by 50% Hepatic: Consider dose reduction Mild-Moderate impairment max dose 300 mg / day	• PR Prolongation • Hypotension
Levetiracetam (Keppra)	IV Load: 60 mg/kg Max Load: 4500 mg Rate: 2-5 mg/kg/min Usually given over 15 minutes Doses ≤ 1500 mg can be given IV push over 2-5 minutes. Doses > 1500 mg should be given as IV piggyback. Maintenance: 750-2000 mg IV BID Use actual body weight	SV2A receptor modulator. Suggested to involve inhibition of N-time calcium channels, facilitation of GABA-ergic inhibitor transmission, reduction of delayed rectifier potassium current, binding to synaptic proteins modulating neurotransmitter release.	Renal: 67% Enzymatic Hydrolysis: 33%	6-8	< 10%	None	25-60 mg/L Unclear relationship between serum levels and efficacy. Dose guided by clinical response	Renal: Consider dose reduction HD: 50% removed dose, add 50% of AM dose to PM dose post-dialysis. Consider 1000 mg daily with additional 500 mg dose pose HD sessions. CRRT: Consider increase in total daily dose by 50% Hepatic: Consider dose reduction by 50% in severe impairment	• Sedation • Minimal drug interactions

Medication	Initial, Loading and Maintenance Dosing	Mechanism of Action	Method of Inactivation	Half-Life (hr)	Protein Binding	Drug Interaction	Targeted Drug Levels	Dose Adjustments	• Side Effects / Monitoring / Nursing Considerations
Lorazepam (Ativan)	IV Load: 0.1 mg/kg Max: 4 mg Give at a rate of 2 mg/min May repeat dose in 5-10 minutes Use actual body weight	Benzodiazepine Enhances the inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride ions.	Hepatic Metabolism	12-14	85-91%	Serum Concentrations increased by: Valproic Acid and derivatives,		Renal: None Liver: None	• Hypotension • Respiratory Depression • Dilute 1:1 with NS • IV contains propylene glycol
Midazolam (Versed)	IV Load: 0.2 mg/kg Max: 10 mg Give IV Push over 2 minutes May epeat dose every 5 minutes until seizures stop: 0.2-0.4 mg/kg up to a max total loading dose of 2 mg/kg IV Infusion: 0.2-2.9 mg/kg/hr Typical Starting Dose: 0.2 mg/kg/hr IM: 0.2 mg/kg, Max: 10mg Intranasal: 10 mg Use actual body weight	Benzodiazepine Enhances the inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride ions.	Hepatic Metabolism Active metabolite undergoes renal excretion	3-11	95%	Inhibitor of: CYP3A4, 2C9, 2C8 Metabolism induced by: Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin		Renal: Consider dose reduction due to active metabolite accumulation HD/CRRT: None Hepatic: Consider dose reduction	• Hypotension • Respiratory depression • Accumulates in adipose tissue • Active metabolite • Short duration of effect with initial doses, may accumulate with repeated doses or continuous infusion

Medication	Initial, Loading and Maintenance Dosing	Mechanism of Action	Method of Inactivation	Half-Life (hr)	Protein Binding	Drug Interaction	Targeted Drug Levels	Dose Adjustments	• Side Effects / Monitoring / Nursing Considerations
PENTObarbital (Nembutal)	IV Load: 5-15 mg/kg Max rate of 50 mg/min. Max single loading dose: 1000 mg May repeat loading dose of 5-10 mg/kg until seizures stop Initial IV Infusion Rate: 1 mg/kg/hr Maintenance Infusion: 0.5-5 mg/kg/hr Typical Starting Dose: 0.5 mg/kg/hr Breakthrough SE: 5 mg/kg bolus, increase CI rate by 0.5-1 mg/kg/hr every 12 hours as needed Use actual body weight	Barbiturate Exhibits GABA-like effects	Hepatic Metabolism	15-50	35-55%	Inducer of: CYP3A4, A6 VPA may increase the serum concentration of barbiturates.	Hypnotic: 1-5 mg/L Coma: 10-50 mg/L	Renal: None HD: None Hepatic: Consider dose reduction	• Hypotension • Gastric stasis / ileus • Myocardial depression • Thrombocytopenia • Metabolic acidosis • Requires mechanical ventilation • At high doses, can cause complete loss of neurologic function • IV contains propylene glycol
PHENObarbital (Luminal)	IV Load: 20 mg/kg Max: 2000 mg Give at a rate of 50-100 mg/min. May repeat Loading dose in 10 minutes: 5-10 mg/kg Maintenance Dose: 1-3 mg/kg/day in 2-3 divided doses Use actual body weight	Barbiturate Exhibits GABA-like effects	Hepatic: 75% Renal: 25%	53-140	20-45%	Inducer of: UGT, CYP3A4, 2B6, 2C9, 2A6, 1A2 Metabolism induced by: Carbamazepine Serum concentration increased by: Fosphenytoin, Phenytoin VPA may increase the serum concentration of barbiturates.	20-50 mg/L	Renal: Consider dose reduction HD: Give PM dose after HD Hepatic: Consider dose reduction	• Hypotension • Respiratory depression • Metabolic acidosis • IV contains propylene glycol

Medication	Initial, Loading and Maintenance Dosing	Mechanism of Action	Method of Inactivation	Half-Life (hr)	Protein Binding	Drug Interaction	Targeted Drug Levels	Dose Adjustments	• Side Effects / Monitoring / Nursing Considerations
PHENYtoin (Dilantin)	IV Load: 20 mg/kg Infuse at a maximum rate of 50 mg/min May repeat loading dose in 10 min: 5-10 mg/kg Maintenance Dosing: 100 mg IV TID Use actual body weight	Enhances sodium efflux from neurons of the motor cortex, stabilizing the threshold against excitability	Hepatic Metabolism	10-15 (IV)	90%	Inducer of: CYP1A2, 2B6, 2C, 3A3, 3A4, 3A5, 3A6, 3A7 Metabolism induced by: Carbamazepine Serum Concentration reduced by: Phenobarbital Serum concentrations increased by: benzodiazepines	Total: 15-25 mcg/mL Free: 1.5-2.5 mcg/mL Monitor free level when on VPA, BZD, other highly protein bound drugs, low albumin or critically ill	Renal: None HD: None Hepatic: Consider dose reduction	• Arrhythmia • Hypotension • Purple glove syndrome • Metabolic acidosis • Must use IV filter • Avoid small vein IVs • Only compatible with NS • Precipitates with other drugs and diluents, including D5W, potassium, insulin, heparin, norepinephrine, cephalosporins, dobutamine
Propofol (Diprivan)	IV Load: 1-2 mg/kg Give IV load over 3-5 minutes Max Loading Dose: 10 mg/kg Initial Rate: 30 mcg/kg/min Bolus and increase rate until seizure control Maintenance Infusion: 10-200 mcg/kg/min Breakthrough SE: Increase CI rate by 5-10 mcg/kg/min every 5 min or 1 mg/kg bolus plus CI titration Use actual body weight	Anesthetic. Produces CNS depression, presumably through GABA-A receptor agonism and/or NMDA receptor blockade.	Hepatic Metabolism	4-7 (can be up to1-3 days)	90%			Renal: None HD: Unclear but probably none Liver: None	• Hypotension • Hypertriglyceridemia • Propofol infusion syndrome (metabolic acidosis, bradycardia, cardiac arrest, rhabdomyolysis) • Change IV tubing every 12 hours • Monitor pH, bicarb, CPK and cardiac function • Accumulates in adipose tissue • Contraindications: soy / egg allergy • Avoid doses > 83 mcg/kg/min for > 24-48 hours
Topiramate (Topamax) **NG/PO Only**	Initial Dosing: 200-400 mg NG/PO Maintenance: 300-1600 mg / day in 2-4 divided doses	Blocks neuronal voltage-dependent sodium channels, enhances GABA-A activity, antagonizes AMPA/kainate glutamate receptors, inhibits carbonic anhydrase.	Renal: 70% Hepatic: not extensive	21	15-41%	Weak Inducer of: CYP 3A4 Weak Inhibitor of: CYP 2C19 Metabolism induced by: Carbamazepine Serum concentration decreased by: Fosphenytoin, Phenytoin May enhance the effects of VPA, including hyperammonemia, hepatic dysfunction and hypothermia.		Renal: CrCl < 70: decrease dose by 50% HD: Supplemental dose may be required Metabolic acidosis: Consider dose reduction	• Metabolic acidosis • No IV formulation

Medication	Initial, Loading and Maintenance Dosing	Mechanism of Action	Method of Inactivation	Half-Life (hr)	Protein Binding	Drug Interaction	Targeted Drug Levels	Dose Adjustments	• Side Effects / Monitoring / Nursing Considerations
Valproate Sodium (Depacon)	IV Load: 40 mg/kg Max: 3000 mg Give IV Load over 10 minutes at a rate of 3-6 mg/kg/min. Maintenance: 10-15 mg/kg/day IV in 2-3 divided doses Use actual body weight	Increases availability of GABA. May enhance action of GABA or mimic its action at postsynaptic receptor sites.	Hepatic Metabolism	9-16	90%	Weak Inhibitor of: CYP2C19, 2A6, 3A4 Weak Inducer of: CYP2A6 Serum conc. reduced by: Barbiturates Carbapenems Metabolism increased by: Carbamazepine Increases serum concentrations of: Carbamazepine metabolites, barbiturates Displaces phenytoin from protein binding sites. Inhibits CYP metabolism of: Phenytoin, Lamotrigine	Total: 80-140 mg/L Free: 4-11 mg/L Only consider if toxicity suspected	Renal: None HD: None Hepatic: Avoid	• Hyperammonemia • Pancreatitis • Thrombocytopenia • Hepatotoxicity • Use with caution in patients with TBI • May be a preferred agent for glioblastoma multiforme

Approved by:

_____	_____
Neeraj Badjatia, MD, Medical Director	Brigid Blaber, MS, RN, PCS Manager

Revised 10/2012: Gunjan Parikh, MD; Jennifer Hopp, MD Carla Peterman, PharmD; Colleen Gaffney, NP; Lila Motemaden, RN; Mary Ann Bautista, RN
Revised 12/2017: Gunjan Parikh, MD; Michael Armahizer, PharmD;
Revised 3/2020: Peter Crino MD; Jennifer Hopp, MD; Stephanie Chen, MD; Camilo Gutierrez, MD; Neeraj Badjatia, MD; Nicholas A. Morris, MD; Wendy Chang, MD; Melissa Motta, MD; Gunjan Parikh, MD; Michael Armahizer, PharmD

References

Alldredge, B. (2001). A Comparison of Lorazepam, Diazepam, and Placebo for the Treatment of Out-of-Hospital Status Epilepticus. *New England Journal of Medicine*, 631-37.

Brophy GM, B. R. (2012). Guidelines for the Evaluation and Management of Status Epilepticus. *Neurocrit Care*.

Chen JWY, W. C. (2006). Status epilepticus: pathophysiology and management in adults. *Lancet Neurology, 5*(3), 246-256.

Claassen J, S. R. (2012). Emergency Neurologic Life Support: Status Epilepticus. *Neurocrit Care*, S73-S78.

Fernandez A, C. J. (2012). Refractory status epilepticus. *Curr Opin Crit Care, 18*, 127-131.

Jensen S, G. E. (2006). How long do most seizures last? A systematic comparision of seizures recoreded in the epilepsy monitoring unit. *Epilepsia, 47*(9), 1499-1503.

Kapur J, E. J. (2019). Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med, 381*, 2103-13.

Karnad DR, G. K. (2008). Neurologic disorders in pregnancy. *Crit Care Med, 33*(10), S362-371.

Kramer AH. (2012). Early ketamine to treat refractory status epilepticus. *Neurocrit Care*, 299-305.

Krishnamurthy KB, D. F. (1999). Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. *Epilepsia, 40*, 759-762.

Molgaard-Nielsen. (2011). Newer-generation antiepileptic drugs and the risk of major birth defects. *J Am Med Assoc, 305*(19), 1996-2002.

Rossetti AO, L. G. (2005). Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol, 62*, 1698-1702.

Voss LJ, S. J. (2008). The howling cortex: seizures and general anesthetic drugs. *Anesth Analg*, 1689-1703.