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SUMMARY

Status epilepticus is a subset of seizures defined by prolonged seizure activity and is considered a neurologic emergency. Neurologic insults such as stroke or head trauma can place patients at significant risk for the development of status epilepticus (1). In severe traumatic brain injury patients, seizures or status epilepticus occurs in 20-30% of patients during the acute phase (2). Therefore, rapid identification and treatment is critical. Prompt administration of benzodiazepines is the first line treatment for both convulsive (CSE) and non-convulsive status epilepticus (NCSE) with additional treatment with anti-epileptic medications (3).

RECOMMENDATIONS

- **Level 1**
 - **Benzodiazepines (BZD) are the first line treatment for status epilepticus (NCSE).**
 - **Lorazepam 4 mg IV Q 5 min x 2 doses**
OR
Midazolam 5-10 mg IV Q 5 min x 2 doses
 - **NO IV ACCESS: Midazolam 10 mg IM/IN (intra-nasal)/ IO(intraosseus) Q 5 min x 2 doses**
- **Level 2**
 - **Urgent control antiepileptic drug (AED) should be initiated as soon as the first BZD dose is administered.**
 - **If HOME AED is available IV – use as first line urgent control therapy at an appropriate dose**
 - **First choice (no or unknown home AED): Levetiracetam 60 mg/kg (max 4.5g) IVPB x 1**
 - **Continuous electroencephalogram (cEEG) monitoring should be initiated on all patients in CSE / NCSE.**
- **Level 3**
 - **A step-wise approach is recommended to the management of patients in refractory CSE / NCSE.**
 - **cEEG should be read frequently and as clinically indicated for patients in NCSE to facilitate timely therapy adjustments for the management of ongoing seizures.**

INTRODUCTION

Patients with convulsive or non-convulsive (electrographic) status epilepticus (SE) should receive immediate treatment. Rapid administration of a BZD is first line followed by urgent control therapy with a maintenance antiepileptic drug (AED) (3-6). It is important to recognize that the dosing of BZD and/or continuous infusion anesthetic agents for the treatment of SE, refractory SE (RSE) or super-refractory SE (SRSE) is much higher than

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based on the medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

that utilized for ICU sedation and that initiation and all dose changes should be preceded by a bolus dose of the agent. A *stepwise approach to management of seizures is outlined on pages 2, 3 and 4.*

DEFINITIONS & ABBREVIATIONS (3-5):

- **AED = anti-epileptic drug**
- **BZD = benzodiazepine**
- **EEG = electroencephalogram**
- **cEEG = continuous electroencephalogram**
- **CSE = Convulsive Status Epilepticus** – continuous clinical seizure activity lasting ≥ 5 minutes OR recurrent seizure activity without recovery of consciousness between seizures.
- **NCSE = Non-Convulsive Status Epilepticus** – continuous or recurrent electrographic seizure activity on cEEG without evidence of clinical seizures
- **SCC** – Surgical Critical Care

Management of Acute CONVULSIVE or NON-CONVULSIVE Status Epilepticus in the Traumatic Brain Injury Patient

TIER 1									
<p>1. Benzodiazepine IV-push Q 5 min x 2 doses</p> <p>a. Lorazepam (Ativan®) 4 mg IV Q 5 min x 2 doses OR</p> <p>b. Midazolam (Versed®) 5-10 mg IV Q 5 min x 2 doses</p> <p>No IV Access:</p> <p>c. Midazolam 10 mg IM/IN/IO Q 5 min x 2 doses</p> <p><u>AND</u></p> <p>2. START urgent control medication with HOME AED <u>OR</u> Levetiracetam</p> <p>a. Give <u>AS SOON AS FIRST</u> BZD dose administered</p> <p>b. Levetiracetam 60 mg/kg (max 4.5g) IVPB x1; then 1 g IV Q 8 hrs</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="background-color: #ffff00;">Checklist for the 1st Hour</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/> POCT blood glucose</td> </tr> <tr> <td><input type="checkbox"/> Monitor pulse oximetry, BP, cardiac monitoring, EKG, and give supplemental O₂ and fluids PRN</td> </tr> <tr> <td><input type="checkbox"/> Labs: CBC, BMP, Ca, Mag, AED levels (if appropriate), toxicology screen, blood cx (if febrile)</td> </tr> <tr> <td><input type="checkbox"/> Head CT</td> </tr> <tr> <td><input type="checkbox"/> STAT spot EEG and then initiate cEEG monitoring</td> </tr> <tr> <td><input type="checkbox"/> Consult Neurology</td> </tr> <tr> <td><input type="checkbox"/> Consider LP or CSF Culture</td> </tr> </tbody> </table>	Checklist for the 1st Hour	<input type="checkbox"/> POCT blood glucose	<input type="checkbox"/> Monitor pulse oximetry, BP, cardiac monitoring, EKG, and give supplemental O ₂ and fluids PRN	<input type="checkbox"/> Labs: CBC, BMP, Ca, Mag, AED levels (if appropriate), toxicology screen, blood cx (if febrile)	<input type="checkbox"/> Head CT	<input type="checkbox"/> STAT spot EEG and then initiate cEEG monitoring	<input type="checkbox"/> Consult Neurology	<input type="checkbox"/> Consider LP or CSF Culture
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<p><u>CSE ONLY: Continues to seize 5 min after 2nd BZD dose?</u></p> <ul style="list-style-type: none"> • REPEAT BZD dose x 2 <p><u>NCSE or CSE after repeated BZD therapy → continues to seize?</u></p> <ul style="list-style-type: none"> • Advanced airway to allow sedative drip initiation and titration • ADD second AED NOTE: Do <u>NOT</u> use fosphenytoin and valproic acid together – serious drug interactions. <ul style="list-style-type: none"> ○ Fosphenytoin (Cerebyx®) 20 mg/kg IVPB x 1, then 5 mg/kg/day divided Q 8 hrs <ul style="list-style-type: none"> ▪ Check Free Phenytoin Calculated level 2 hours after loading dose (Goal Free 1-2 mcg/mL) AND/OR ▪ Check TROUGH Free Phenytoin Calculated level after 24 hours (Goal Free 1-2 mcg/mL) ▪ See Appendix “A” for level management recommendations <p><u>OR</u></p> <ul style="list-style-type: none"> ○ Valproic acid (Depakote®) 40 mg/kg IVPB x 1, then 30 mg/kg/day divided Q 8 hrs <i>*Preferred for patients with a diagnosis of primary generalized epilepsy</i> <ul style="list-style-type: none"> ▪ Check valproic acid TROUGH level after 24 hours (Goal 50-100 mcg/mL) ▪ See appendix “A” for level management recommendations ▪ Check LFTs and ammonia level Q 48 hrs (or more frequently if elevated) <ul style="list-style-type: none"> • MOVE to Tier 2 									

TIER 2

Initiate Midazolam (Versed®) Bolus + Drip

1. Midazolam (Versed) 0.2 mg/kg IV-push bolus, then start at 0.2 mg/kg/hr, Titrate to burst suppression 3-5 bursts / minute
2. Re-bolus with midazolam 0.1 mg/kg (from the pump) and increase drip by 0.1 mg/kg/hr Q 3 hrs to maintain burst suppression (max dose 2 mg/kg/hr)
3. May bolus from the pump (0.1mg/kg) Q 30 min PRN to maintain burst suppression
4. **Call Neurology to read cEEG if not burst suppressed at midazolam 1 mg/kg/hr**

CSE: move to Tier 3 if continues to have clinical seizures when midazolam rate ≥ 1 mg/kg/hr

NCSE: cEEG read still (+) for seizures: Joint discussion between SCC & Neurology & move to Tier 3

TIER 3

1. **ADD third AED:** Lacosamide (Vimpat®) 400 mg IV x1, then 200 mg IV Q 12 hrs
2. **Initiate Ketamine Bolus + Drip (If CONTRAINDICATED: maximize Versed to 2 mg/kg/hr)**
 - a. Criteria:
 - i. Continuous EEG (cEEG) – (+) seizures
 - ii. Midazolam (Versed) drip rate ≥ 1.0 mg/kg/hr
 - b. Ketamine Dosing:
 - i. BOLUS: Ketamine 2 mg/kg IV-push x 1
 - ii. Infusion: Ketamine 1 mg/kg/hr – titrate by 0.5 mg/kg/hr to burst suppression 3-5 bursts / minute (max 7.5 mg/kg/hr)
 - iii. Re-bolus ketamine 1 mg/kg IV - push with each dose change
3. **Call Neurology to read cEEG if not burst suppressed at Ketamine 5 mg/kg/hr**

cEEG read still (+) for seizures: Joint discussion between SCC & Neurology & move to Tier 4

TIER 4

1. **ADD fourth AED:** Phenobarbital 20mg/kg, then 1-4 mg/kg IV Q 12 hrs
**Note: Drug interaction with valproic acid, trough levels of both agents should be assessed.*
 - i. Check **TROUGH** phenobarbital level after 24 hours (Goal 20-40 mcg/mL)
 - ii. See appendix "A" for level management recommendations
2. **Initiate Propofol Bolus (MD Only) + Drip**
 - a. Criteria:
 - i. cEEG (+) seizures
 - ii. Midazolam (Versed) drip rate ≥ 1.0 mg/kg/hr
 - iii. \pm Ketamine drip rate ≥ 5 mg/kg/hr
 - b. Propofol Dosing:
 - i. BOLUS (*MD to Administer*): Propofol 1-2 mg/kg IV-push x 1
 - ii. Infusion: Propofol 50 mcg/kg/min – titrate by 10 mcg/kg/min to burst suppression (3-5 bursts/minute) on cEEG (max 100 mcg/kg/min)
 - iii. Daily Monitoring: Labs (CK, lactic acid, triglyceride levels); EKG (for QTc)
**Patient will likely require vasopressor support due to the high doses of Propofol*

Continues to have seizures on cEEG on maximally tolerated propofol?

Joint discussion between SCC & Neurology & move to Tier 5

IMPORTANT: On all Tiers – scheduled AEDs monitored utilizing serum concentrations should be titrated to the targeted therapeutic range – dose adjustments may be made utilizing recommendations in Appendix A and/or working with your clinical pharmacist to optimize therapy.

****Transition to Tier 5 should be a joint discussion & decision between Neurology and SCC****
A clear evaluation of the risks and benefits should be assessed before initiating pentobarbital

TIER 5

Initiate Pentobarbital (Nembutal®) Bolus + Drip

1. Criteria:
 - a. cEEG still (+) for seizures
 - b. Patient maximized on ≥ 4 AED **AND** ≥ 2 continuous infusions at max doses
2. Pentobarbital Dosing:
 - a. BOLUS: 10 mg/kg IVPB x1
 - b. Infusion: 1 mg/kg/hr titrate by 1 mg/kg/hr Q 1 hr to burst suppression (3-5 bursts/min) on cEEG read (max 5 mg/kg/h)
 - c. Bolus 5mg/kg IVPB x 1 PRN for breakthrough seizures
 - d. Wean off midazolam / ketamine / propofol after infusion started – continue ALL other AEDs
 - i. Recommend weaning off other infusions in reverse order of initiation
 - ii. Midazolam last to wean off
 - e. Continue frequent cEEG reads until burst suppression achieved
 - f. Continue therapy for 48 hours after burst suppression achieved
 - g. **RESUME** midazolam infusion (bolus 0.2 mg/kg IV-push, start at 0.2 mg/kg/hr) prior to weaning pentobarbital off (high-risk of recurrent seizures during wean)

SEIZURES RESOLVED – WEANING RECOMMENDATIONS

1. Continue all therapy, at current doses, for 24-48 hours after clinical and/or electrographic resolution of seizures.
2. Maintain cEEG monitoring while weaning continuous infusions.
3. Weaning Recommendations:
 - a. Continuous Infusions – wean rate Q 3 hrs until off; one agent at a time
 - b. Drug weaning recommendations – wean off in this order as applicable:
 - i. Pentobarbital – wean by 0.5mg/kg/h Q 3 hrs until off (REMINDER: restart midazolam drip @ 0.2 mg/kg/hr (with 0.2 mg/kg IV bolus) before starting wean)
 - ii. Propofol – wean by 10 mcg/kg/min Q 3 hrs until off
 - iii. Ketamine – wean by 0.5 mg/kg/hr Q 3 hrs until off
 - iv. Midazolam – wean by 0.05-0.1 mg/kg/hr Q 3 hrs until off
4. Continue all scheduled AEDs, unchanged, while weaning off continuous infusion.

LITERATURE REVIEW:

The management of patients with status epilepticus (SE) should proceed rapidly but with consideration to maximizing therapy, achieving cessation of seizure activity and limiting adverse events associated with anti-epileptic drug (AED) therapy. As defined by the Commission of Classification and Terminology of the International League Against Epilepsy (ILAE), there are two time points to consider in the management of status epilepticus, time point T1 and time point T2. Time point T1 is the time when seizures do not stop spontaneously, which is 5 minutes for tonic-clonic (convulsive) seizures and 10 minutes for focal status epilepticus with or without impairment of consciousness and absences. At T1, the diagnosis of status epilepticus is established, and treatment is initiated. Time point T2 is when neuronal damage begins to occur, 30 minutes for bilateral tonic-clonic seizures and 60 minutes for focal status epilepticus. At T2, treatment should prevent neuronal damage (7).

Initial management should begin with aggressive benzodiazepine (BZD) dosing (e.g. lorazepam 4 mg IV-push Q 5-10 min) (3,4,6). Urgent control therapy should also be instituted – current literature supports the use of fosphenytoin (or phenytoin), levetiracetam, valproic acid or phenobarbital (3-6,8). Given the minimal side effects and lack of drug interactions with levetiracetam, it may be reasonable as a first line agent (9). Chakravarthi et al. compared levetiracetam (20 mg/kg) to phenytoin (20 mg/kg) in 44 patients as first line therapy after benzodiazepine and found no statistical difference in rate of seizure cessation (59% levetiracetam vs. 68% phenytoin, $p=0.53$) (10). A meta-analysis by Yasiry et al. revealed a wide range of response to AED therapy in patients who fail initial BZD treatment. Response rates were as follows: levetiracetam 68.5% (56.2-78.7%), phenobarbital 73.6% (58.3-84.8%), phenytoin 50.2% (43.2-66.1%) and valproic acid 75.7% (63.7-84.8%). The data in this meta-analysis was limited primarily to retrospective or observational studies except for valproic acid but suggests similar efficacy among these three agents (11). The ESETT trial by Kapur et al. demonstrated the clinical equivalence of fosphenytoin 20 mg PE/kg, levetiracetam 60 mg/kg and valproate 40 mg/kg as second line agents (after administration of BZD). The primary outcome of this study looked at the absence of clinical seizure within 60 minutes after administration of the drug (12).

For patients who persist in CSE/NCSE, intubation and initiation of a continuous infusion anesthetic (preceded by a bolus dose) (5). Patients' whose therapy is unsuccessful after treatment with a benzodiazepine and one anti-seizure medication is considered refractory status epilepticus (7). The most commonly recommended continuous infusion AEDs are midazolam, propofol and pentobarbital (5). The key to successful termination of seizure activity with any of these agents is the administration of a bolus dose prior to the start of the infusion (NOTE: in Florida, only physicians or nurse anesthetists may bolus propofol) (3,13,14). In contrast to ICU sedation dosing and consistent with the Neurocritical Care Society recommendations, continuous infusion midazolam for status epilepticus should be weight-based with a bolus of 0.2 mg/kg and then an initial infusion rate of 0.2 mg/kg/hr titrated to a maximum of 2 mg/kg/hr; a bolus of 0.1mg/kg should precede all dose increases (6). Similarly, propofol may require infusion rates as high as 200 mcg/kg/min to achieve burst suppression. These high rates do carry a higher risk of propofol infusion syndrome and daily monitoring of QTc interval, serum creatinine kinase and triglyceride levels should accompany all infusions that exceed 50 mcg/kg/min (6,10). More recently, ketamine, which targets N-methyl-d-aspartate (NMDA) receptors rather than gamma-aminobutyric acid (GABA), has demonstrated efficacy in controlling seizures that have persisted more than 60 minutes. This is due to a down regulation of GABA and upregulation of NMDA the longer a patient continues to seize (17). Additionally, ketamine also does not have the hypotension and cardiac depression associated particularly with propofol and pentobarbital (midazolam may cause hypotension) (13,14). Ketamine may still pose a risk of emergence reactions, but co-administration or bolus-dose administration of midazolam should mitigate this response (14-16). For ketamine and midazolam, in particular, all dose changes should be preceded by a bolus dose. Due to the multitude of complications associated with its as well as its prolonged duration of action, pentobarbital infusions should be considered a last resort in patients refractory to all other therapies.

The use of lacosamide for the management of status epilepticus is an area of on-going research. Newey et al. retrospectively evaluated the effectiveness of lacosamide for refractory SE. These patients were on an average of 2.4 AEDs prior to the initiation of lacosamide. The authors reported that 58.8% had cessation of SE at 24 hours after lacosamide initiation and this increased to 82.4% at 48 hours. The authors also reviewed the safety and noted no significant increase in the PR-interval on EKG; mild transaminitis was reported in 8/84 patients but may have been caused by concurrent AEDs (18). In 2018, Husain et al. conducted a prospective, multicenter, randomized controlled trial comparing the use of lacosamide to fosphenytoin for the treatment of non-convulsive seizures. The study did exclude patients with convulsive seizures or seizures lasting more than thirty minutes. The authors found that lacosamide was non-inferior to fosphenytoin with respect to seizure cessation (63.3% vs. 50%, p=0.02). There was no significant difference between the two groups with respect to requiring rebolus or a second agent. This study is limited in that it excluded patients with prolonged seizures (19).

For patients in SE, medication optimization is important. Correct timing of trough concentrations for fosphenytoin (or phenytoin) and valproic acid assists with appropriately assessing and adjusting the dose. Total phenytoin levels should be drawn concurrent with a serum albumin level just prior to a dose and the dose should be correct for albumin levels < 3.5 mg/dL for more accurate assessment. The goal total corrected phenytoin level is 10-20 mcg/mL. At Orlando Health, order a "Free Phenytoin Calculated" level provides a total phenytoin level, serum albumin and a calculated free level – providing a more complete assessment of the patient. Ideally, in critically ill patients, a serum free phenytoin trough concentration would be the most preferred. Similarly, valproic acid levels should also be drawn as a trough and adjusted to achieve a target of 50-100 mcg/mL (20).

NCSE and Seizures in Traumatic Brain Injury:

In 20-30% of traumatic brain injured (TBI) patients, human studies demonstrate convulsive seizures or NCSE while in the acute phase after injury. For 33% of patients, NCSE or convulsive seizures presents within the first three days following a traumatic injury. The rat model study by Andrade et al. demonstrated seizures within the first 72 hours for the traumatic brain injured group. In the TBI group, lateral fluid-percussion injury demonstrated a NCSE with additional behavioral changes (2). In a large cohort study from the National Trauma Data Bank of the USA, the type of traumatic hemorrhage as well as the presenting GCS of the patient were found to have varying risks of seizures development after TBI. Moderate TBI (GCS 9-12) was found to have the greatest risk of seizure at 0.8%. Finally, while subarachnoid and subdural hemorrhages were associated with an increased risk of seizures; however, no association was found with epidural and intraparenchymal hemorrhages (21).

APPENDIX A: Antiepileptic Drug Monitoring

Fosphenytoin / Phenytoin (PTN)

- Free phenytoin level **2 hours after** administration of the loading dose(s)
- Non-loading doses / maintenance doses: order phenytoin **TROUGH** level (wait at least 24 hours after loading dose before ordering a trough)

Free PTN Level* (mcg/mL)	No Seizure Activity	Ongoing Seizure Activity
< 0.5	Reload 20 mg/kg	Reload 20 mg/kg
0.5-1	Reload 10 mg/kg	Reload 10 mg/kg
1.0-2.0	No change	Mini-load according to the equation below to optimize level between 2-2.5 mcg/mL**
2.0-2.5	No change or decrease maintenance doses if AEs present	No change Consider additional AED
> 2.5	Decrease maintenance regimen	No change or decrease maintenance doses if AEs present

AED = antiepileptic drug; AE = adverse events

*Trough level or 2 hour post-load level

**Mini-Loading Dose:

$$\text{Fosphenytoin / Phenytoin (mg)} = (\text{Desired Free Level} - \text{Actual Free Level}) \times 10 \times \text{weight (kg)} \times 0.7$$

Valproic Acid and derivatives (VPA):

- Total valproic acid level **1 hours after** administration of the loading dose(s)
- Non-loading doses / maintenance doses: order valproic acid **TROUGH** level (wait at least 24 hours after loading dose before ordering a trough)

Total VPA Level (mcg/mL)	No Seizure Activity	Ongoing Seizure Activity
< 10	Reload 20-40 mg/kg	Reload 20-40 mg/kg
10-50	Reload 10-20 mg/kg	Reload 10-20 mg/kg
50-100	No change	Mini-load according to the equation below to optimize level between 100-150 mcg/mL**
100-150	No change or decrease maintenance doses if AEs present	No change Consider additional AED
> 150	Decrease maintenance regimen	No change or decrease maintenance doses if AEs present

**Mini-Loading Dose: VPA (mg) = (Desired level – Actual level) x weight (kg) x 0.2

Levetiracetam: Clinical correlation between levels and seizure resolution is not well established

- Target **TROUGH** Levels: 20-40 mcg/mL
- Levels are a SEND-OUT
 - Schedule as a trough before a dose (preferably a morning dose)
 - Order as a miscellaneous level
 - Turn around 24-72 hours
- Consider obtaining levels at steady state (2-3 days into therapy) in the following patients:
 - Renal dysfunction / failure
 - Elderly
 - Pregnant women
 - Co-administration with enzyme-inducers (eg. carbamazepine, fosphenytoin, oxcarbazepine, phenobarbital, primidone)

Phenobarbital Levels

- Target **TROUGH** Levels: 20-40 mcg/mL
- Draw as a trough **BEFORE** a dose (wait at least 24 hours after loading dose before ordering a trough)

Total Phenobarbital Level (mcg/mL)	No Seizure Activity	Ongoing Seizure Activity
< 10	Reload 20 mg/kg	Reload 20 mg/kg
10-20	Continue current dose	Reload 10mg/kg Increase maintenance dose ~25%
20-40	Continue current dose	Mini-load according to the equation below to optimize level between 30-40 mcg/mL**
> 40	Decrease maintenance regimen ~25%	No change or decrease maintenance doses if AEs present

**Mini-Load =
$$\frac{(\text{Desired level} - \text{Actual level}) \times 0.7 \text{ L/kg} \times \text{Weight (kg)}}{0.9}$$

Pentobarbital: Clinical correlation between levels and seizure resolution is not well established

- Target **TROUGH** Levels for *Therapeutic Coma*: 20-40 mcg/mL
- SEND OUT to Mayo Jacksonville
- Only run on Mondays and Wednesdays – ~1 week turn around
- Only send if need confirmation for withdrawal of life support discussions

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