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Management of Status Epilepticus in Adults

Evidence Based Medicine Guideline

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SUMMARY
Status epilepticus (SE) 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. Rapid identification and prompt treatment, starting with benzodiazepines (BZD), is critical. Of note, the dosing of benzodiazepines and/or continuous infusion anesthetic agents for the treatment of SE, refractory SE (RSE) or super-refractory SE (SRSE) is much higher than 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 the management of seizures is outlined.

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 (intraosseous) Q 5 min x 2 doses**
- **Level 2**
  - **Urgent control antiseizure medication (ASM) should be initiated as soon as the first BZD dose is administered.**
    - **If HOME ASM is available IV – use as first-line urgent control therapy at an appropriate dose**
    - **First choice (no or unknown home ASM): Levetiracetam 60 mg/kg (max 4.5 g) IVPB x 1**
  - **Continuous electroencephalogram (cEEG) monitoring should be initiated on all patients in SE**
- **Level 3**
  - **A stepwise approach to the management of patients in refractory SE should be implemented.**
  - **cEEG should be read frequently and as clinically indicated for patients in SE to facilitate timely therapy adjustments for the management of ongoing seizures.**
  - **Once SE resolves, continuous infusion anesthetics should be weaned off; controller ASMs should be continued.**

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.

INTRODUCTION

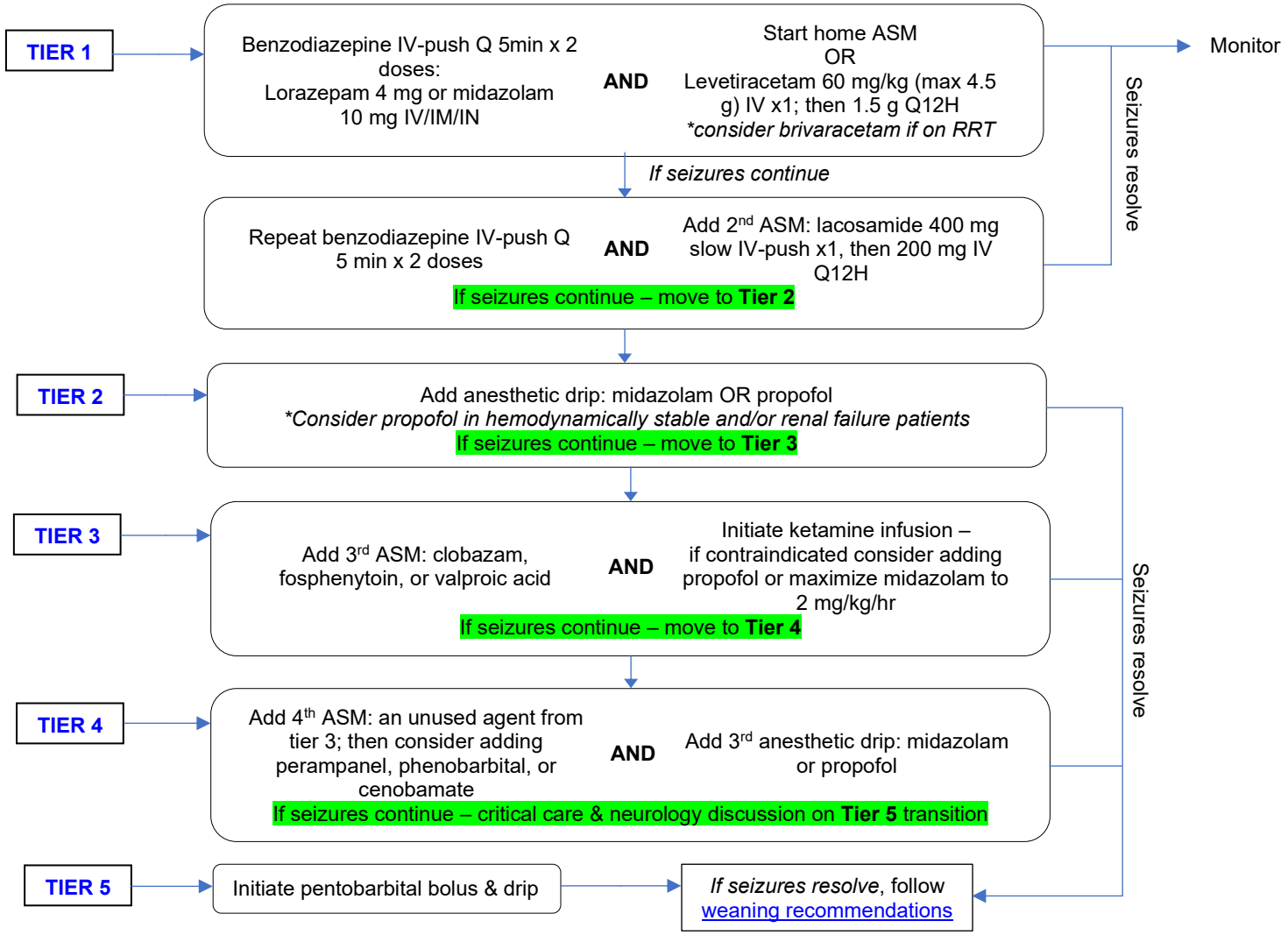
Patients with convulsive or non-convulsive (electrographic) status epilepticus (SE) should receive immediate treatment. Rapid administration of a BZD is first-line followed by urgent control therapy with a maintenance antiseizure medication (ASM) (1-6). It is important to recognize that the dosing of BZD and/or continuous infusion anesthetic agents for the treatment of SE, refractory SE (RSE) or super-refractory SE (SRSE) is much higher than that utilized for ICU sedation. *A stepwise approach to management of seizures is outlined on pages 2-6.*

DEFINITIONS & ABBREVIATIONS (3-5):

- ASM = anti-seizure medication
- BZD = benzodiazepine
- EEG = electroencephalogram
- cEEG = continuous electroencephalogram
- SE = 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 Status Epilepticus Flow Diagram

**Not intended for treatment of post-arrest myoclonic status or epilepsia partialis continua (EPC)*



Management of Acute Status Epilepticus in the Traumatic Brain Injury Patient

*Not intended for treatment of post-arrest myoclonic status or epilepsia partialis continua (EPC)

TIER 1

1. **Benzodiazepine IV-push Q 5 min x 2 doses**
   a. Lorazepam (Ativan®) **4 mg** IV Q 5 min x 2 doses
   OR
   b. Midazolam (Versed®) **5-10 mg** IV Q 5 min x 2 doses
   No IV Access:
   c. Midazolam **10 mg** IM/IN/IO Q 5 min x 2 doses

AND

2. **START urgent control medication with HOME ASM OR Levetiracetam**
   a. Give ***AS SOON AS FIRST*** BZD dose administered
   b. Levetiracetam 60 mg/kg (max 4.5 g) IVPB x1; then 1.5 g IV Q12H (1 g IV Q8H for CrCl > 130 mL/min)
   [1] Must renally adjust maintenance dose
   [2] Consider brivaracetam as an alternative in patients on renal replacement therapy

Checklist for the 1st Hour
☐ POCT blood glucose
☐ Monitor pulse oximetry, BP, cardiac monitoring, EKG, and give supplemental O_2 and fluids PRN
☐ Labs: CBC, BMP, Ca, Mag, AED levels (if appropriate), toxicology screen, blood cx (if febrile)
☐ Head CT
☐ STAT spot EEG and then initiate cEEG monitoring
☐ Consult Neurology
☐ Consider LP or CSF Culture

SE ONLY: Continues to have clinical seizures 5 min after 2nd BZD dose?

- ***REPEAT Benzodiazepine IV-push Q5min x 2 doses (doses as above)***

AND

3. **ADD second ASM**
   Lacosamide (Vimpat®) 400 mg slow IV-push x 1, then 200mg IV Q12H
   [1] Must renally adjust maintenance dose
   Note: Obtain an ECG 1 hour after administration. If PR interval on baseline ECG is > 180 ms, use an alternative second ASM agent.

Continues to seize?

- ***Advanced airway to allow sedative drip initiation and titration***
- *Move to Tier 2*

[1] See Appendix B for renal dose adjustment
[2] Can consider brivaracetam (Briviact®) in select patients (e.g. Renal failure, HD patients):

- LD: 200 – 400 mg and MD: 50 – 100 mg Q12H
- In hepatic dysfunction (Child Pugh A, B, C): 25 – 75 mg Q12H

Tier 2

ADD Anesthetic Drip
Midazolam (Versed®) Bolus + Drip

a. Midazolam (Versed®) 0.2 mg/kg IV-push Bolus, then start at 0.2 mg/kg/hr, titrate to cessation of clinical seizures or burst suppression (2 – 3 bursts per 15 seconds [1 screen])
b. Re-bolus with midazolam 0.1 mg/kg (from the pump) Q30 minutes if not meeting titration parameter
    i. If patient has a convulsive seizure, can give an additional bolus and contact MD
c. May increase drip by 0.1 mg/kg/hr Q3H to cessation of clinical seizures (max dose 2 mg/kg/hr)
d. Continuous EEG (cEEG) – read as frequently as clinically necessary until resolution of seizures – **call Neurology for read if still seizing at midazolam 1mg/kg/hour**

OR

Propofol Bolus (MD Only) + Drip – consider in hemodynamically stable and/or renal failure patients

a. Criteria:
    i. Continuous EEG (cEEG) – read every 1- 2 hours until resolution of seizures – **call Neurology for read**
b. Propofol Dosing:
    i. *Optional* 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 cessation of clinical seizures (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*

If EEG comes back with no seizures, then stop titration of anesthetic agent
Move to Tier 3 if continues to have clinical seizures when midazolam rate ≥ 1.0 mg/kg/hr

Tier 3

ADD Third ASM:
*NOTE: Do **NOT** use fosphenytoin and valproic acid together – serious drug interactions.*

Clobazam (Onfi®)10 – 20 mg PO x1, then 10 – 20 mg/day divided in 1-2 doses (max 60mg /day)

a. Doses > 30 mg should be divided Q12H
b. CYP2C19 inhibitors will increase clobazam concentrations
c. Clobazam levels (parent & metabolite) are send out levels to monitor for toxicity
    i. Clobazam (parent drug) goal level: 30 – 300 ng/mL
    ii. N-desmethylcobazam (metabolite) goal level: 300 – 3000 ng/mL

OR

Fosphenytoin (Cerebyx®) 20 mg/kg IVPB x1, then 5mg/kg/day divided Q8H

a. Check Calculated Free Phenytoin level 2 hours after loading dose
b. (Goal Free 1-2 mcg/mL) **AND/OR**
c. Check Calculated Free Phenytoin **TROUGH** level after 24 hours of therapy
d. (Goal Free 1-2 mcg/mL)
e. See Appendix A for level management recommendations

OR

Tier 3 Continued on page 5 …

Tier 3 Continued…

Valproic acid (Depakote®) 40 mg/kg IVPB x1, then 30 mg/kg/day divided Q8H
CANNOT use if patient has received a dose of a carbapenem within the last 14 days
**Preferred for patients with a diagnosis of primary generalized epilepsy*

a. Check valproic acid total **TROUGH** level after 24 hours (Goal 50-100 mcg/mL or Free 5-25 mcg/mL)
b. Check valproic acid **FREE** level if patient has renal dysfunction and/or shows signs/symptoms of toxicity (Goal 5-25 mcg/mL)
c. Check LFTs and ammonia level Q 48h (or more frequently if elevated)
d. See Appendix A for level management recommendations

AND

Initiate Ketamine Bolus + Drip (*If CONTRAINDICATED [3]: consider adding propofol or maximize midazolam to 2mg/kg/hour)*

a. Criteria:
   i. Continuous EEG (cEEG) – read as frequently as clinically necessary until resolution of seizures – **call Neurology for read**
   ii. Midazolam (Versed) drip rate ≥ 1.0 mg/kg/hr
b. Ketamine Dosing:
   i. BOLUS: Ketamine 1 mg/kg IV-push x 1
   ii. Infusion: Ketamine 0.5 mg/kg/hr – titrate by 0.5 mg/kg/hr to cessation of clinical seizures (max 7.5 mg/kg/hr)
   iii. Re-bolus ketamine 1 mg/kg IV - push with each dose change

If EEG comes back with no seizures, then stop titration of anesthetic agent
Move to Tier 4 if continues to have clinical seizures when ketamine rate ≥ 5 mg/kg/hr

[3] Contraindications to Ketamine infusion: uncontrollable hypertension, uncontrolled intracranial hypertension

TIER 4

ADD Fourth ASM:
NOTE: Drug interaction with phenobarbital and valproic acid, trough levels of both agents should be assessed.
Add one of the unused agents from Tier 3 (preferred)

a. Reminder: **DO NOT** combine valproic acid and fosphenytoin

THEN consider adding

Perampanel (Fycompa®) PO ONLY

a. Dosing dependent on if taking concomitant CYP3A4 inducer[4]
   i. NOT on enzyme inducer: perampanel 2 mg PO QHS (max 12mg)
   ii. On concomitant CYP3A4 inducer: perampanel 4 mg PO QHS (max 12mg)
b. Avoid in patients with psychiatric disorders (black box warning)

OR

Phenobarbital 20mg/kg, then 1-4 mg/kg IV Q12H

a. Check **TROUGH** phenobarbital level after 24 hours (Goal 20-40 mcg/mL)
b. See Appendix A for level management recommendations

OR

Tier 4 Continued on page 6 …

Tier 4 Continued…

Cenobamate (Xcopri®) PO ONLY: 12.5 – 200mg PO daily (weekly titrations)
a. Not recommended in ESRD
b. Slow titration is required to avoid risk of Stevens-Johnson syndrome

AND ADD 3rd Anesthetic Drip

Midazolam (Versed®) Bolus + Drip
a. Refer to **Tier 2** for monitoring parameters

OR

Propofol Bolus (MD Only) + Drip – consider in hemodynamically stable and/or renal failure patients
a. Refer to **Tier 2** for monitoring parameters

If EEG comes back with no seizures, then stop titration of anesthetic agent
Continues to have clinical seizures on maximally tolerated anesthetics? Discuss Tier 5.

[4] CYP3A4 Inducers = phenytoin. Carbamazepine, and oxcarbazepine

***IMPORTANT*: On all Tiers** – *scheduled ASMs 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*****

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: 0.5 mg/kg/hr titrate by 0.5 mg/kg/hr Q 1H to burst suppression (2 – 3 bursts per 15 seconds [1 screen]) on cEEG read (max 4 mg/kg/h)
   c. Bolus 5mg/kg IVPB x1 PRN for breakthrough seizures
   d. Wean off midazolam / ketamine / propofol after infusion started – *continue* ALL other ASMs
   e. Continue Q6H cEEG reads until burst suppression achieved
   f. Continue therapy for 48 hours after burst suppression achieved
   g. ***At time of pentobarbital weaning,***
      i. ***RESUME*** midazolam infusion (bolus 0.2 mg/kg, start at 0.2 mg/kg/h do not titrate) prior to weaning pentobarbital off (high-risk of recurrent seizures during wean)
      ii. Wean pentobarbital by 0.5 mg/kg/h Q1H until off

SEIZURES RESOLVED – WEANING RECOMMENDATIONS

1. Continue all therapy, at current doses, for 24 hours after clinical and/or electrographic resolution of seizures.
2. Maintain cEEG monitoring 24 – 48 hours after continuous infusions have been weaned off.
3. Weaning Recommendations:
   a. Continuous Infusions – wean rate until off; one agent at a time
   b. Drug weaning recommendations – wean off in the reverse order as initiated
      i. Ketamine – wean by 0.5 mg/kg/hr Q1H until off
      ii. Midazolam – wean by 0.1 mg/kg/hr Q1H until off
      iii. Propofol – wean by 10 mcg/kg/min Q1H until off
4. Continue all scheduled ASMs, 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 antiseizure medications (ASM) therapy. Initial management should begin with aggressive benzodiazepine (BZD) dosing (e.g. lorazepam 4 mg IV-push Q 5-10min) (1-4). Urgent control therapy should also be instituted – current literature supports the use of fosphenytoin (or phenytoin), levetiracetam, valproic acid or phenobarbital (1-5). Given the minimal side effects and lack of drug interactions with levetiracetam, it may be reasonable as a first-line agent (6). 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) (7). A meta-analysis by Yasiry et al. revealed a wide range of responses to ASM 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 (8).

For patients who persist in SE, intubation and initiation of a continuous infusion anesthetic (preceded by a bolus dose). The most recommended continuous infusion anesthetics are midazolam, propofol, ketamine, and pentobarbital (1). 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) (1,9,10). 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/hour titrated to a maximum of 2 mg/kg/hour; a bolus of 0.1 mg/kg should precede all dose increases (4). Similarly, propofol may require infusion rates as high as 200 mcg/kg/min to achieve burst suppression (2 – 3 bursts per 15 seconds [1 screen]). 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 (4,7). More recently, ketamine, which targets N-methyl-d-aspartate (NMDA) receptors rather than gamma-amingobutyric acid (GABA), has demonstrated efficacy in controlling seizures that have persisted more than 60 minutes. Additionally, ketamine does not have the hypotension and cardiac depression associated particularly with propofol and pentobarbital (midazolam may cause hypotension) (10,11). Ketamine may still pose a risk of emergence reactions but co-administration or bolus administration of midazolam should mitigate this response (10-12). For ketamine and midazolam in particular, all dose changes should be preceded by a bolus dose. Due to the multitude of associated complications 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 (13). These patients were on an average of 2.4 ASMs 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 ASMs (13). 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 when administered as the first agent (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 (14).

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 concurrently with a serum albumin level just prior to a dose and the dose should be corrected 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, ordering 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 (15).

APPENDIX A: Antiepileptic Drug Monitoring (15-17)

Clobazam:

- Target levels (parent & metabolite):
  - Clobazam (parent drug): 30 – 300 ng/mL
  - N-desmethylclobazam (metabolite): 300 – 3000 ng/mL
- CYP2C19 inhibitors will increase clobazam concentrations
- *Levels are a SEND-OUT*
  - Order as a miscellaneous level

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:
Fosphenytoin / Phenytoin (mg) = (Desired Free Level – Actual Free Level) x 10 x weight (kg) x 0.7

Free Fosphenytoin Levels: **Target Range 1-2 mcg/mL**

Consider for the patients with the following risk factors for increased free fraction:

1. Critically ill
2. Hypoalbuminemia (Albumin < 3 mg/dL)
3. Renal dysfunction (CrCl < 20 mL/min and/or on renal replacement therapy)
4. Significant drug-drug interactions (e.g. valproic acid)

Levels are a SEND-OUT to Mayo Clinic

1. Order as a miscellaneous lab
2. Schedule as a trough before a dose (preferably a morning dose)
3. Turn around is ~48 hours – when sent Monday – Friday
4. Requires a red or green-top container

Lacosamide: Clinical correlation between levels and seizure resolution is not well established; oversedation is associated with level > 10 mcg/mL

- Target **TROUGH** Levels: 1-10 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

Levetiracetam: Clinical correlation between levels and seizure resolution is not well established; oversedation is associated with levels > 40 mcg/mL

- Target **TROUGH** Levels: 10-40 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)

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

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 10 mg/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 = $\frac{\text{(Desired level – Actual level) x 0.7 L/kg x Weight (kg)}}{0.9}$

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

Free Valproic Acid Levels: **Target Range 5-25 mcg/mL**

Consider for the patients with the following risk factors for increased free fraction:

1. Critically ill
2. Hypoalbuminemia (Albumin < 3 mg/dL)
3. Renal dysfunction (CrCl < 20 mL/min and/or on renal replacement therapy)
4. Significant drug-drug interactions (e.g. fosphenytoin)
5. Total valproic acid < 50 mg/dL despite appropriate dosing

Levels are a SEND-OUT to Mayo Clinic

1. Order as a miscellaneous lab
2. Schedule as a trough before a dose (preferably a morning dose)
3. Turn around is ~48 hours – when sent Monday – Friday

APPENDIX B: Antiseizure Medication Renal Dose Adjustments (15-17)

Antiseizure Medication	CrCl mL/min/1.73m^2	Dose Adjustment
Brivaracetam (Briviact®)	---	No dosage adjustment necessary
Cenobamate (Xcopri®)	ESRD	Use not recommended
Clobazam (Onfi®)	---	No dosage adjustment necessary
Fosphenytoin (Cerebyx®)	---	No dosage adjustment necessary
Lacosamide (Vimpat®)	< 30 HD CRRT	75% of the max dose 75% of the max dose, with a supplemental dose (up to 50%) after each HD session No dose adjustment (increase if adjusted for HD)
Levetiracetam (Keppra®)	80 to 130 50 to <80 30 to <50 15 to <30 <15 HD CRRT	500 mg – 1.5 g Q12H 500 mg – 1.5 g Q12H 250 – 750 mg Q12H 250 – 500 mg Q12H 250 – 500 mg Q24H 250 – 500 mg supplemental dose may be needed 750 – 1250 mg Q12H (up to 2000 mg Q12H
Perampanel (Fycompa®)	< 30 HD	Use not recommended Use not recommended
Phenobarbital	< 10 HD CRRT	50 – 66% of usual dose 50 – 66% of usual dose. May require supplemental dose 50% of usual dose No dose adjustment necessary
Valproic acid (Depakote®)	< 10 HD CRRT	Monitor clinical response. Monitor free valproic acid levels if necessary

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