STATUS EPILEPTICUS

ALGORITHM 1. PHASES OF CLINICAL MANAGEMENT

Utilize the **Neuro IP Status Epilepticus (First Line Orders)** and **Neuro IP Status Epilepticus (Infusion Orders)** in Epic to guide anticonvulsant therapy

Inclusion criteria:

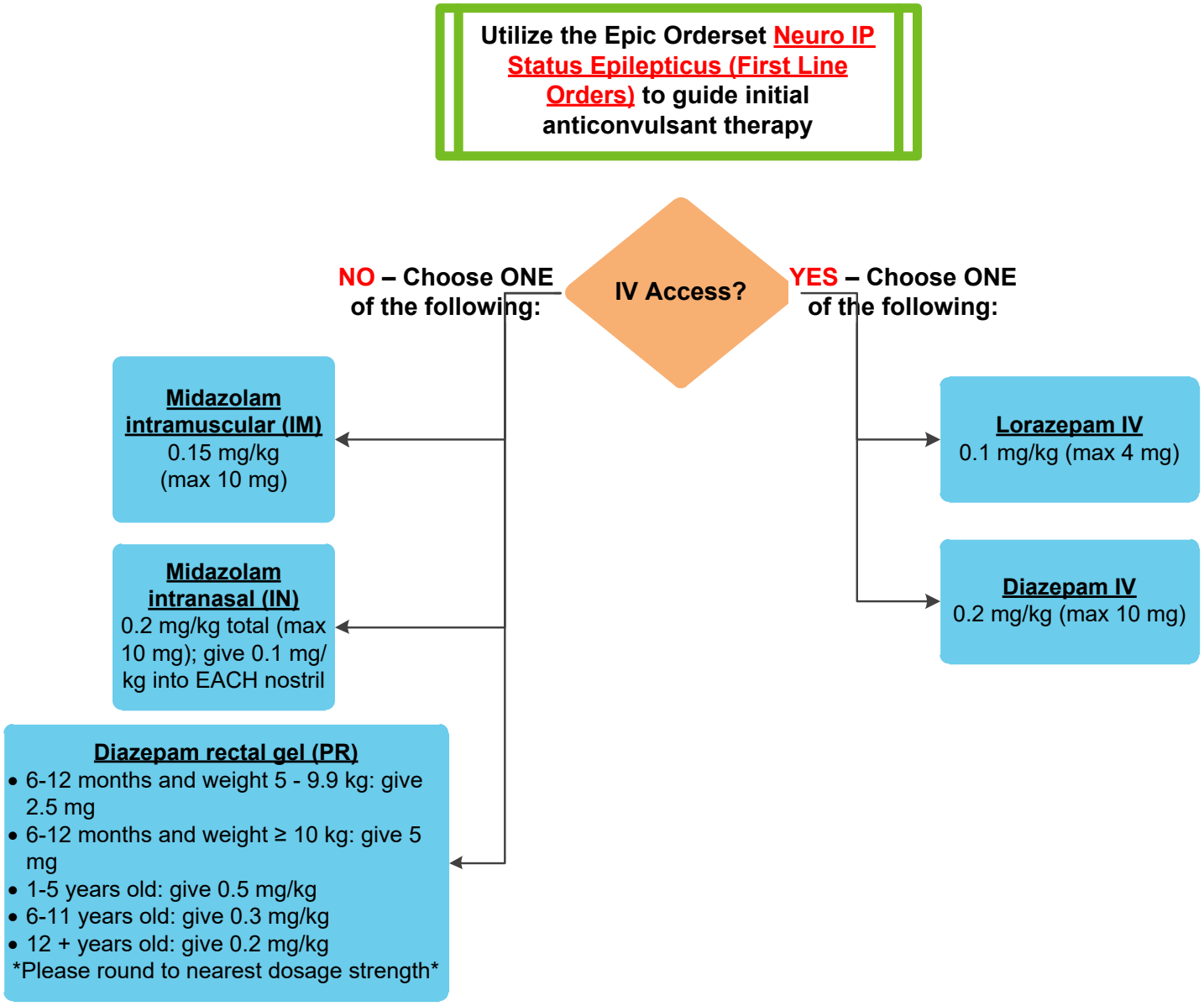
- Continuous clinical seizure activity
- Intermittent seizure activity without a return to clinical baseline between seizures
- Confirmed continuous seizure activity on patients undergoing an EEG

Exclusion criteria:

- Neonates less than 28 days old
- Children with diagnosed non-epileptic events and strong suspicion that events are non-epileptic in origin

0-5 minutes	Stabilization Phase	• Stabilize patient (airway, breathing, circulation) • Fingerstick blood glucose. Treat if less than 60 mg/dL • Attempt IV access and collect electrolytes, hematology, toxicology screen, anticonvulsant levels (if appropriate)
5-20 minutes	First Line Therapy Phase	• Administer benzodiazepine, route based on presence of IV access (refer to First Line Agent Dosing Algorithm)
20-40 minutes	Second Line Therapy Phase	• Administer second line agent: fosphenytoin, levetiracetam, phenobarbital, or valproate sodium (refer to Second Line Agent Dosing Algorithm)
40-60 minutes	Third Line Therapy Phase	**Note**: Consider additional second line agents or benzodiazepines while working to initiate continuous infusion. • Administer continuous intravenous agent: midazolam, pentobarbital, ketamine, or propofol (refer to Third Line Agent Dosing Algorithms)

ALGORITHM 2. FIRST LINE AGENT DOSING



ALGORITHM 3. SECOND LINE AGENT DOSING

Utilize the Epic Orderset Neuro IP Status Epilepticus (First Line Orders) to guide initial anticonvulsant therapy

When advancing to a second-line agent:

- Under most circumstances, **choose ONE** of the following second line agents

Fosphenytoin

- 20 mg PE/kg (max 1500 mg PE) over 15 minutes
- If no effect 10 minutes after infusion is completed, consider additional 10 mg PE/ kg load

Levetiracetam

- 60 mg/kg (max 4500 mg) over 15 minutes

Phenobarbital

- Particularly in younger infants
- 20 mg/kg (max 1000 mg) over 15 minutes
- If no effect 10 minutes after infusion is completed, consider additional 10 mg/kg load

Valproate Sodium

- Particularly in absence status epilepticus
- 40 mg/kg (max 3000 mg) over 15 minutes
- Avoid in children less than 2 years old.

If seizures persist 10-20 minutes after the second-line agent finishes infusing:

- Strongly consider advancing to a continuous infusion agent to improve the likelihood of quickly achieving seizure control
- Consult Neurology and the PICU
- Consider STAT Extended Inpatient EEG Order

ALGORITHM 4. CONTINUOUS INFUSION AGENT DOSING

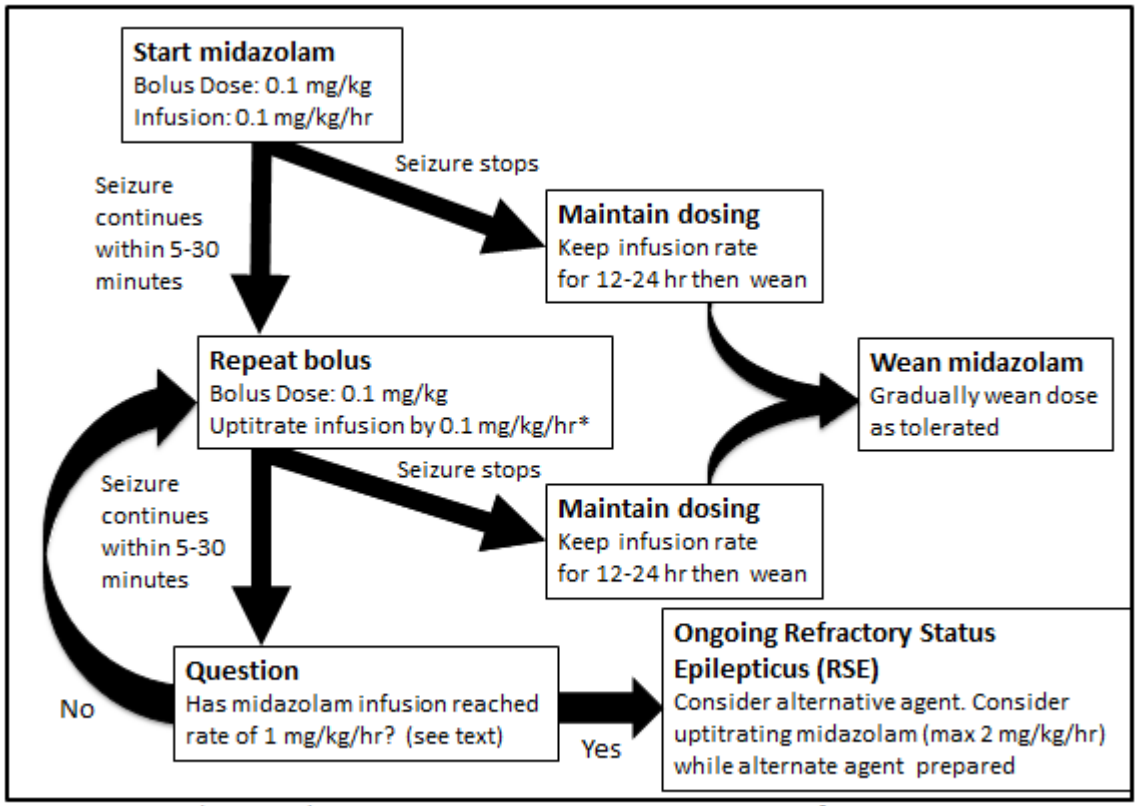
Adapted from Tasker & Vitali (2014)

Continuous Infusion Therapy Phase:

Note: Consult Neurology and the PICU

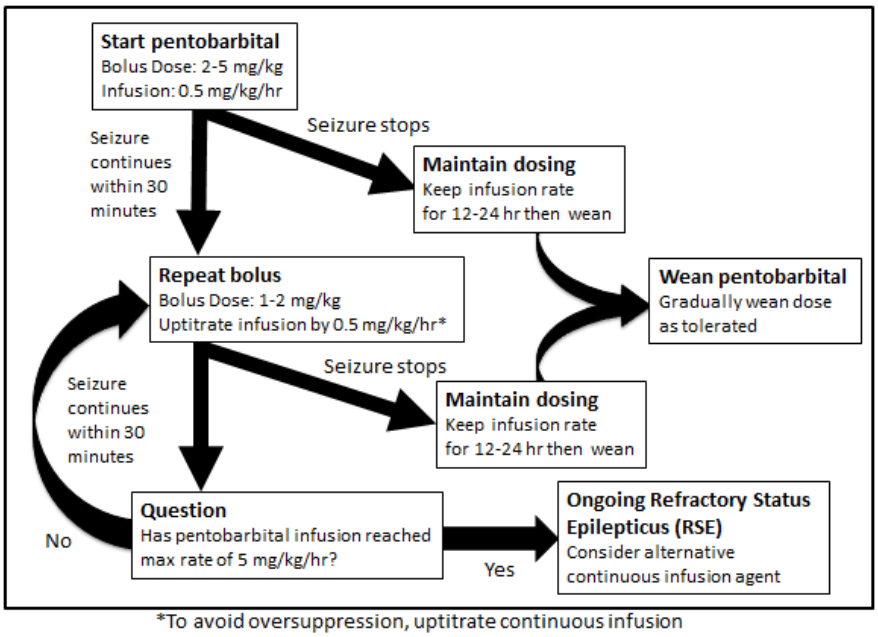
- The following Continuous Infusion Agents should be strongly considered if seizures persist 10-20 minutes after the second-line agent has finished infusing.
- **Utilize the Epic Orderset Neuro IP Status Epilepticus (Infusion Orders) to guide anticonvulsant therapy.**
- **Choose ONE** of the following four options for the continuous infusion therapy phase (midazolam, pentobarbital, propofol, or ketamine) and follow the associated treatment and dosing algorithm.

A. MIDAZOLAM



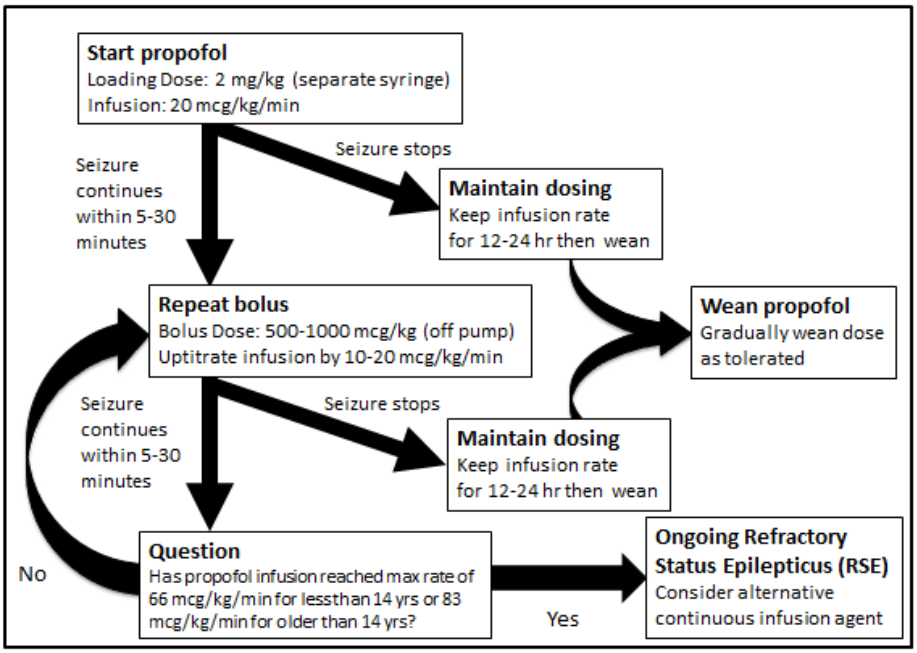
*To avoid oversuppression, uptitrate continuous infusion sparingly (e.g., by 0.1 mg/kg/hr every other bolus)

B. PENTOBARBITAL

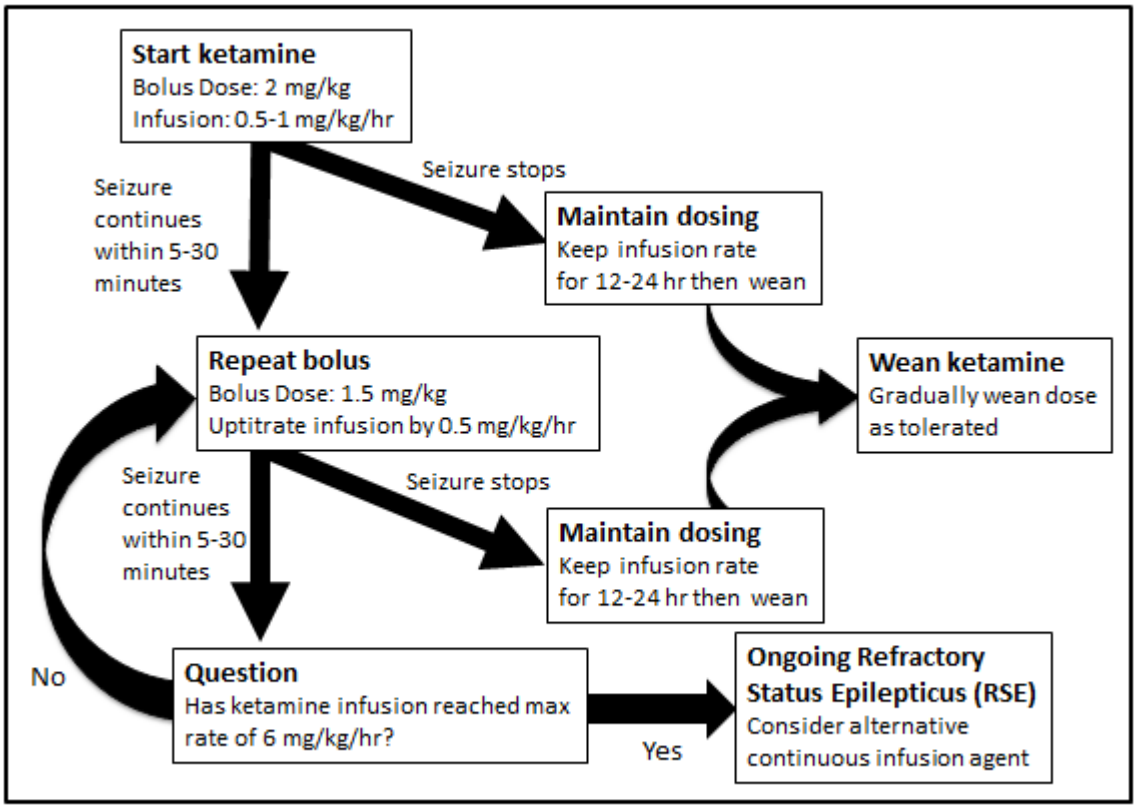


*To avoid oversuppression, uptitrate continuous infusion sparingly (e.g., by 0.5 mg/kg/hr every other bolus)

C. PROPOFOL



D. KETAMINE


Start ketamine
Bolus Dose: 2 mg/kg
Infusion: 0.5-1 mg/kg/hr
Seizure stops
Seizure continues within 5-30 minutes
Maintain dosing
Keep infusion rate for 12-24 hr then wean
Wean ketamine
Gradually wean dose as tolerated
Repeat bolus
Bolus Dose: 1.5 mg/kg
Uptitrate infusion by 0.5 mg/kg/hr
Seizure stops
Seizure continues within 5-30 minutes
Maintain dosing
Keep infusion rate for 12-24 hr then wean
No
Question
Has ketamine infusion reached max rate of 6 mg/kg/hr?
Yes
Ongoing Refractory Status Epilepticus (RSE)
Consider alternative continuous infusion agent

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TARGET POPULATION

Inclusion Criteria

This protocol should be utilized in the following clinical situations in either inpatient or outpatient settings when applicable, regardless of suspected etiology:

- Continuous clinical seizure activity
- Intermittent seizure activity without a return toward clinical baseline between seizures
- Confirmed continuous seizure activity on patients undergoing an electroencephalogram (EEG)

Exclusion Criteria

The following groups of patients should be excluded from this protocol

- Neonates less than 28 days old
- Children with diagnosed non-epileptic events OR strong suspicion that events are non-epileptic in origin

BACKGROUND | DEFINITIONS

Status epilepticus (SE) is one of the most common pediatric neurological emergencies. Patient age, etiology, and SE duration all affect outcome, but only SE duration can be modified with timely administration of anticonvulsant medications. Benzodiazepine receptors internalize during prolonged seizures, stressing the importance of early treatment while the receptor is available to bind the medication. In a study of 190 pediatric patients with status epilepticus, a longer time to benzodiazepine and non-benzodiazepine administration were associated with a longer duration of status epilepticus. [1] Utilizing a standardized clinical pathway may help reduce status epilepticus duration and morbidity. The American Academy of Neurology has established a quality measurement set that recommends that patients start third-line therapy within 60 minutes of seizure onset or arrival to the emergency department (ED). [4]

Definitions

Status epilepticus - a continuous seizure lasting ≥5 minutes or two or more discrete seizures between which there is incomplete recovery of consciousness. [2]

Refractory status epilepticus - Clinical or electrographic seizures that persist after an adequate dose of an initial benzodiazepine and a second appropriate anti-seizure medication. [3]

INITIAL EVALUATION

The initial evaluation of the patient presenting in status epilepticus centers on prompt stabilization of the patient, cessation of seizure activity, and determination of the etiology of the patient's seizures.

Stabilization

- Patients presenting in status epilepticus are at high risk for cardiopulmonary failure secondary to ongoing seizure activity, as well as side effects of antiepileptic medications. Careful adherence to resuscitation and PALS protocols is paramount.
    - Initiate continuous pulse oximetry and cardiac monitoring, as well as frequent blood pressure monitoring.
    - Assess oxygenation and respiratory effort. Administer oxygen as needed for hypoxia if respiratory effort is adequate. Frequent reassessment for hypopnea or apnea should be completed for all patients on oxygen, especially those with escalating oxygen requirements. Consider intubation if patient has signs of respiratory compromise, including hypopnea/apnea, irregular respiratory effort, poor secretion management, and/or compromised cough or gag reflexes.
    - Consider continuous capnography.
- Obtain IV access. If unable to obtain PIV, consider IO placement.

History and Physical

- If caregivers are present or the medical record can be quickly reviewed, determine if the patient has a known history of seizures or epilepsy. The most common etiologies of status epilepticus in patients with known seizures or epilepsy include breakthrough seizure, missed medication, and illness. Thus, patients with known seizures may not require extensive work-up; however, work-up should always be tailored to the individual patient.
- Common etiologies of new onset status epilepticus include hypoglycemia, electrolyte disturbances, drug/toxin ingestion, intracranial pathology (such as intracranial hemorrhage, stroke, or tumor), CNS infection, febrile status epilepticus, and undiagnosed epilepsy.
- Screen for fever, illness, dehydration, exposure, ingestion, trauma, or fall. If signs or symptoms noted on physical exam and history are suggestive of a provoking etiology, consider the evaluations below.

Diagnostic Work-Up for Status Epilepticus

Hypoglycemia – ANY patient is at risk for hypoglycemia (including patients with known epilepsy).

- Check blood glucose and correct if less than 60 mg/dL (5 mL/kg [max: 150 mL per dose of 10% dextrose (D10)]).
    - If patient is on ketogenic diet, correct blood glucose only if less than 40 mg/dL with 2.5 mL/kg D10.
- Consider empiric Thiamine 20 mg/kg/day IV prior to dextrose if at risk for nutritional deficiencies.

Electrolyte disturbances – Particularly important to consider for infants and patients with recent vomiting, diarrhea, or poor PO intake.

- Check basic or comprehensive metabolic panel (BMP or CMP) to assess for hyponatremia or hypocalcemia.
- Correct hyponatremia carefully (goal to increase sodium to 120 mEq/L quickly then slowly increase by less than 8-12 mEq/L/day) to mitigate risk of cerebral pontine demyelination.
    - Administer hypertonic saline 3 mL/kg of 3% (0.5 mEq/mL Na+))

    - Repeat plasma sodium, and if remains low and the patient is seizing, repeat the dose.
- Correct hypocalcemia with calcium gluconate (or calcium chloride if central venous line (CVL) in place) and consider assessing for concurrent hypomagnesemia.

Drug/toxin ingestion – Consider in patients with possible exposure.

- Blood gas to evaluate for acidosis, which could suggest ingestion
- UTox, salicylate, acetaminophen, and ethanol levels
- EKG

Sub-therapeutic anticonvulsant serum concentrations – Consider in patients with a history of epilepsy on anticonvulsant therapy.

- Consider checking anticonvulsant drug concentrations in situations where compliance may be a concern (e.g. – emesis, teenager, etc.).
- If serum concentrations are subtherapeutic, discuss dosage change with the pediatric neurology team.

Intracranial pathology – Strongly consider for infants, patients with concern for head trauma or significant fall, patients with focal seizure, patients with focal neurologic deficits, patients with signs of increased intracranial pressure, and patients with poor return to baseline after cessation of seizure activity.

- Consider emergent non-contrast head CT or rapid MRI brain protocol.

Additional Diagnostic Considerations

Electroencephalogram (EEG)

- To assess for subclinical seizure activity and assist in medication titration, an EEG should be ordered STAT after failure of the second-line agent or if the patient is paralyzed before clinical seizure activity stops (ex. For rapid sequence intubation).
- Place the Extended Inpatient EEG Order in EPIC and page Neurology ICU resident/APP or Neurology on-call resident to notify of need for STAT EEG. The Neurology team is responsible for triaging EEGs and will contact the EEG technologists
- However, do not postpone imaging or lumbar puncture for the EEG unless directed to do so by the Neurology or ICU team.

Infectious evaluation – if patient is febrile or clinical history is suggestive of infection:

- Obtain CBC with differential, BMP, CRP, ESR, 2 blood cultures, serum save and freeze, urinalysis with microscopy and urine culture, respiratory multiplex PCR pathogen panel.
- If head CT/MRI does not show signs of elevated ICP, consider obtaining CSF (cerebrospinal fluid) via lumbar puncture (LP) or requesting neurosurgery to tap shunt. Obtain four tubes of CSF (volume in fourth tube will be used for infectious disease testing).
    - Obtain serum glucose at same time as LP.
    - CSF studies should include cell count with differential, glucose, protein, and bacterial culture.
    - Consider CSF meningitis/encephalitis multiplex PCR panel (MEP; select automatic order due to concern for encephalopathy/encephalitis). MEP includes HSV testing.
    - In patients with CNS hardware, consider requesting microbiology lab to obtain specialized CSF bacterial cultures to detect slow-growing bacteria (i.e., *P. acnes*).
- If new-onset status epilepticus with fever **OR** high suspicion for CNS infection:

- Recommend Infectious Disease consultation to direct further diagnostic work-up and treatment based on exposures/risk factors. [6] Consider empiric antibiotics (meningitic doses) and acyclovir while above testing is pending. Maintain adequate hydration and monitor renal function closely when starting anti-microbials with risk of nephrotoxicity (such as acyclovir, vancomycin, ceftriaxone). Some antibiotics, such as cefepime and fluoroquinolones, may decrease seizure threshold and induce non-convulsive status epilepticus in some patients. [7] This should be considered when choosing antibiotic coverage or evaluating the underlying etiology of status epilepticus in patients on antibiotic therapy.

If the patient is temperature controlled or on pentobarbital infusion, surveillance blood cultures are recommended every 24 hours. Consider urinalysis if indwelling catheter with culture is suggestive of infection, and tracheal aspirate if change in secretions and/or respiratory status.

Metabolic evaluation

- Consider the following, as indicated by history and physical exam:
  - LFTs, ammonia, anticonvulsant levels, urine/serum toxicology screens
  - Metabolic screen (lactate, pyruvate, creatinine kinase, serum amino acids, urine organic acids)
  - Comprehensive CSF studies (lactate, pyruvate, amino acids, neurotransmitter metabolites) could be considered.
- Consider empiric Pyridoxine 50-100 mg IV for infants and young children, ideally administered while patient is on cEEG. Physician must stay with patient during and for 10 minutes after administration in case of apnea/coma. Check serum AASA level to assess for pyridoxine-dependent epilepsy (note: AASA level is NOT affected by pyridoxine supplementation).

Other considerations

- Autoimmune serum and CSF labs (Serum: Encephalopathy autoimmune evaluation panel through Mayo (ENCES), TSH, anti-TPO, anti-thyroglobulin, ESR, CRP, procalcitonin, ANA panel, oligoclonal bands. CSF: Encephalopathy autoimmune evaluation panel through Mayo (ENCEC), oligoclonal bands, opening pressure, freeze and hold remainder) could be considered.
- Further imaging with full brain MRI (for example, seizure protocol) as indicated.
- Obtain STAT review of outside films by radiology; radiology to page and discuss with PICU and/or Neurology team when reviewed.

CLINICAL MANAGEMENT

Supportive Care Goals

PICU admission is warranted in the setting of hemodynamic instability, impending respiratory failure, or refractory SE with need for third-tier treatment (continuous infusion of medications).

If patient is admitted to the floor and unstable, call the Rapid Response Team (RRT).

- Target seizure cessation **AND** reduction of metabolic stress on injured cells
  - Critical to:
    - Rapidly address seizures
    - Maintain cerebral perfusion by avoiding hypotension
    - Prevent hyperthermia
    - Deliver adequate energy
- Maintain safe airway and assure normal oxygenation and ventilation.
  - Intubation and mechanical ventilation if GCS 3-8 or rapid decline in GCS or concern for loss of airway protective reflexes.

- **Strongly consider pre-emptive intubation and mechanical ventilation when considering continuous infusion agents**
- Target normal perfusion and tissue oxygen delivery as measured by physical exam, normal lactate, and end organ function.
- Target normocapnea (PaCO2 40-45) and normoxia (SpO2 90-99%).

- Maintain normal systemic and cerebral perfusion.
  - Cerebral autoregulation is frequently impaired during prolonged (>20-30 min) SE.
    - Avoid treatment of hypertension until seizures have stopped.
    - Assure adequate intravascular volume.
    - Anticipate and quickly treat medication-related hypotension.
  - Target normal BP for age. Avoid hypotension.
  - Be prepared for hypotension with continuous infusion agents and order vasopressor(s) to bedside.
  - Arterial line monitoring is indicated if hemodynamics are labile or patient is intubated.
  - **Consider arterial line when considering inducing pharmacological coma to allow for optimal mitigation and treatment of medication related hypotension.**
  - Consider obtaining central venous access when inducing pharmacological coma.
  - HOB at 30° - unless etiology is acute stroke, in which case, lay patient flat to improve cerebral perfusion.
- Minimize additional cerebral metabolic demands.
  - Target normothermia (36°C-37.5°C).
    - Consider scheduled antipyretics.
    - If using a cooling blanket, control shivering per TTM order set recommendation.
    - Refer to the Thermoregulation Targeted Temperature Management PICU Policy.
- Optimize fluids, electrolytes and nutrition.
  - Target normal serum sodium concentration (134-145 mmol/L).
  - Target normal serum glucose concentration (80-180 mg/dL).
  - Target euvolemia. Treat hypovolemia. Avoid treating hypervolemia until the patient has been hemodynamically stable for 6 hours (not requiring additional fluid resuscitation or increases in vasoactive agents) and risk of cerebral hypoperfusion has been determined to be minimal.
  - Target early enteral nutrition via naso-enteric feeding tube with goal to initiate enteral feeds within 48 hours of admission.

THERAPEUTICS - ANTICONVULSANT RECOMMENDATIONS

****Please refer to the EPIC Ordersets Neuro IP Status Epilepticus (First-Line Orders) and Neuro IP Status Epilepticus (Infusion Orders) to guide anticonvulsant therapeutics for SE****

Note: Prompt administration is the most critical factor. At this time, there is no evidence to suggest one treatment option over another for any agent. Choice of agent may depend on availability to begin medication in a timely manner, patient's home medications, hemodynamic instability, and provider or institutional experience. Consider contacting Neurology to discuss treatment options if there is uncertainty about how to proceed.

First-Line Agents – Refer to the First-Line Agent Dosing Algorithm

Benzodiazepines are most effective when administered within the first 5-10 minutes of seizure activity, before GABA receptors have internalized. Choose ONE of the following options:

- **Lorazepam IV:** 0.1 mg/kg (max 4 mg) administered over 2 minutes. A second dose can be administered if the seizure persists beyond 3-5 minutes after the first dose.
- **Diazepam IV:** 0.2 mg/kg (max 10 mg) administered over 2 minutes. A second dose can be administered if the seizure persists beyond 3-5 minutes after the first dose.
- **If IV access is not available, choose ONE of the following options:**
  - Midazolam intramuscular: 0.15 mg/kg (max 10 mg)
  - Midazolam intranasal: 0.2 mg/kg total (max 10 mg total), give 0.1 mg/kg into EACH nostril
  - Diazepam rectal gel (PR): 6-12 months and weight 5 to 9.9 kg, give 2.5 mg. 6-12 months and weight ≥10 kg, give 5 mg. 1-5 years old, give 0.5 mg/kg; 6-11 years old, give 0.3 mg/kg; 12+ years old, give 0.2 mg/kg.
    - Please round to nearest available dosage strength.
    - Available as 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg

Second-Line Agents – Refer to the Second-Line Agent Dosing Algorithm

When advancing to a second line agent, consider consulting Neurology and informing the ICU that their care may be needed. Under most circumstances, choose **ONE** of the following second-line agents. If seizures persist 10-20 minutes after the second-line agent finishes infusing, strongly consider advancing to a continuous infusion agent (third-line agent) to improve the likelihood of quickly achieving seizure-control.

- **Fosphenytoin IV load:**
  - Fosphenytoin IV is available in all CHCO locations. Fosphenytoin is dosed in mg of Phenytoin Equivalents (PE).
  - 20 mg PE/kg (max 1500 mg PE), infused over 15 minutes.
  - If seizure persists 10 minutes after initial dose is complete, then can consider additional 10 mg PE/kg load (over 10 minutes) or, if unable to administer second bolus, escalate to third-line agent.
  - Check serum total phenytoin concentrations 2-3 hours after the load.
- **Levetiracetam IV load:**
  - Levetiracetam IV is available in all CHCO locations.
  - 60 mg/kg (max 4500 mg), infused over 15 minutes.
  - If seizure persists 10 minutes after dose complete, then advance to third-line agent.
- **Phenobarbital IV load,** particularly in younger infants
  - Phenobarbital IV is available in all CHCO locations.
  - 20 mg/kg (max 1000 mg), infused over 15 minutes.
  - If seizure persists 10 minutes after dose is complete, then can consider additional 10 mg/kg load (infused over 10 minutes) or, if unable to administer second bolus, escalate to third-line agent.
  - Check serum phenobarbital concentration 2-3 hours after the load.
- **Valproate sodium IV Load** (Depacon – the IV form of enteral medications such as Depakote, Depakene, divalproate sodium, or valproic acid) - particularly effective in absence status epilepticus
  - Valproate sodium is available in all CHCO locations except West campus.
  - 40 mg/kg (max 3000 mg), infused over 15 minutes.
  - Avoid in children less than 2 years old, unless mitochondrial DNA polymerase gamma (POLG1) gene status is known.
  - May cause hyperammonemia.
  - If seizure persists 10 minutes after dose complete, then advance to third-line agent.

Third-Line Agents – Refer to the Continuous Infusion Agent Dosing Algorithm

Refractory status epilepticus will typically not respond to alternative second-line agents. The following Continuous Infusion Agents should be strongly considered if seizures persist 10-20 minutes after the second-line agent has finished infusing. *Additional second-line agents may be administered while preparing to initiate a continuous infusion agent.*

Titrate continuous infusion dosing to cessation of electrographic seizures or burst suppression. In most cases, 24-48 hours of seizure control is recommended prior to slow withdrawal of continuous infusion. To avoid oversuppression, uptitrate continuous infusion sparingly (e.g., increase the infusion rate with every other bolus). Reassess every two hours for oversuppression (less than 1 burst per page on EEG, unless suggested by Neurology). If oversuppressed, decrease the infusion rate by 10-20%.

Hypotension and respiratory failure are common and should be anticipated.

If in the Network of Care (NOC) or admitted to a non-ICU hospital floor, evaluate the need for transfer prior to initiating a third-line agent.

- **Midazolam infusion:**
  - Midazolam is available in all CHCO locations.
  - Administer a 0.1 mg/kg IV bolus (over 2 minutes) and then begin continuous infusion at 0.1 mg/kg/hr.
  - Reassess efficacy every 5-30 mins. If seizures persist, then repeat bolus 0.1 mg/kg IV (over 2 minutes) and uptitrate infusion by 0.1 mg/kg/hr to a max rate of 2 mg/kg/hr. To avoid oversuppression, uptitrate continuous infusion sparingly (e.g. – by 0.1 mg/kg/hr every other bolus).
  - While there is no published limit/maximum to the midazolam dose, a rate of greater than 50 mg/hour would seem excessive and may suggest the need to utilize a different agent.
  - Can give additional 0.1 mg/kg boluses as needed for breakthrough seizures.
  - In cohorts of pediatric patients, initial midazolam loading doses range 0.15-0.5 mg/kg and mean midazolam infusion rates range 0.14-0.84 mg/kg/hr. [8] However, when targeting EEG (vs clinical) endpoints, higher doses, up to 2 mg/kg/hr have been used. In adults, a mean effective midazolam infusion rate of 0.48 mg/kg/hr is reported. [9] Consider moving to an alternative infusion if no response is present with midazolam above 1 mg/kg/hr.
- **Pentobarbital infusion:**
  - Pentobarbital is not available in Network of Care locations.
  - Administer a 2-5 mg/kg IV bolus (over 15 minutes) and then begin continuous infusion at 0.5 mg/kg/hr.
  - Reassess efficacy every 30 minutes. If seizures persist, then rebolus in aliquots of 1-2 mg/kg (infused over 10-15 minutes). To avoid oversuppression, uptitrate continuous infusion sparingly (for example, by 0.5 mg/kg/hr every 60 minutes) to a max rate of 5 mg/kg/hr.
  - Can give additional 1-2 mg/kg boluses as need for breakthrough seizures.
  - Administration of repeated, small bolus doses of pentobarbital is the most effective strategy to achieve seizure cessation or burst suppression during coma induction and can facilitate the use of lower infusion rates/doses, which may avoid oversuppression and unnecessarily prolonged coma. [10,11]
- **Propofol infusion Note that LOADING DOSE is in "mg/kg" and continuous infusion (and subsequent boluses off the pump) are in mcg/kg/min or mcg/kg, respectively.**
  - Propofol is not available in Network of Care locations.
  - Administer a 2 **mg/kg** IV loading dose (over 1-5 minutes) using a separate syringe provided by pharmacy. Ater loading dose, then begin continuous infusion at 20 **mcg/kg/min.**

- Reassess efficacy every 5-30 minutes. If seizures persist, then bolus (off the pump) with 500-1000 **mcg/kg** IV and uptitrate infusion by 10-20 **mcg/kg/min** to a max rate of 66 mcg/kg/min (if less than 14 years old) or 83 mcg/kg/min (if 14 years and older)
- Propofol-associated hypotension is dose dependent and more likely when administering larger or repeated bolus doses.
- If a patient arrives from an outside institution appropriately controlled on propofol, consider continuing for up to 24 hours or at least until EEG is placed and seizure rescue medication plan is determined.
- To minimize risk of propofol infusion syndrome:
  - Infusion duration should be as short as possible, and the dose should not exceed 66 mcg/kg/min (if less than 14 years of age) or 83 mcg/kg/min (if 14 years and older).[12] If more than 48 hours required, then need to assess risk/benefit ratio and inform parents/guardians.
  - Continuus blood pressure and heart rate monitoring is required
  - Serial blood gas monitoring, triglyceride, lactate, serum creatine, AST/ALT and creatinine kinase may be helpful to monitor for a developing metabolic acidosis as an early indication of possible propofol infusion syndrome.
  - Refer to the hospital propofol infusion policy for additional information.

- **Ketamine infusion:**
  - Ketamine is available in all CHCO locations.
  - Administer a 2 mg/kg IV bolus (over 5 minutes) and then begin continuous infusion at 0.5-1 mg/kg/hr.
  - Reassess efficacy every 5-30 minutes. If seizures persist, rebolus with 1.5 mg/kg IV and uptitrate infusion by 0.5 mg/kg/h to a max rate of 6 mg/kg/hr.
  - Can give additional 1.5 mg/kg boluses as needed for breakthrough seizures.

Adjunctive Therapies – Can be utilized in parallel with above treatments and/or in preparation for withdrawal of continuous infusion agents.

- **Valproate sodium:**
  - 40 mg/kg IV load (max dose= 3000 mg), infused over 15 minutes
  - A loading dose may be particularly helpful in patients on valproic acid (Depakote or Depakene) maintenance therapy with subtherapeutic levels.
  - Check serum valproate concentration 2-3 hours after the load.
  - Can consider starting maintenance at 15 mg/kg/day divided q6hours, 12 hours after the load.
  - Avoid in children less than 2 years old unless mitochondrial DNA polymerase gamma (POLG1) gene status is known.
  - May cause hyperammonemia.
- Additional **second-line agents** (IV loads +/- maintenance dosing) - Levetiracetam, fosphenytoin, or phenobarbital. Discuss dosing recommendations with Neurology team.
- **Lacosamide:**
  - 5 mg/kg IV load (max 300 mg), infused over 15 minutes
  - Consider starting maintenance at 3-5 mg/kg/day divided BID, beginning 12 hours after the load. Typical max dose is 10 mg/kg/day.
- **Topiramate:**
  - 5-10 mg/kg enteral load (max 400 mg), using immediate release products
  - Typically start maintenance at 3-5 mg/kg/day divided BID, beginning 12 hours after the load.

- Uptitrate by 2-5 mg/kg/day every 2-7 days to a max of 10-15 mg/kg/day.
- May cause a metabolic acidosis.

- **Magnesium Sulfate:**
  - 25-50 mg/kg IV (Max 2 grams), infused over 30 minutes
  - Consider for patients with POLG1 gene mutations.

Additional therapies, such as the ketogenic diet, inhaled anesthetics, hypothermia, and immune modulating treatments, are beyond the scope of this clinical pathway.

Consideration for tapering of continuous infusions

1. There are no data on the appropriate timing or rate of tapering continuous infusions in the treatment of refractory or super-refractory status epilepticus. The considerations detailed below are based on local expert consensus.
2. Individualized tapering plans should be developed by the multidisciplinary care team, including input from ICU, Neurology, and pharmacists. For patients with multisystem disease or super-refractory status, input from other relevant, involved subspecialty teams may also be valuable.
3. Factors to consider when creating a tapering plan:
   - Duration of therapy: prolonged therapy may need a slower taper schedule.
   - Half-life of continuous infusion agent
   - Availability of timely EEG review for seizure recurrence
   - Clinical factors that may support more aggressive tapering rate, e.g., severe hypotension poorly responsive to inotropic agents
   - Previous continuous infusion tapering failure(s)
   - Confidence that more long-term anticonvulsant medications and therapeutic interventions other than the continuous infusion have been sufficiently optimized to mitigate seizure recurrence risk
4. Prior to initiation of the tapering plan, contingency plans for seizure recurrence should be developed by the multidisciplinary care team. The contingency plan should address:
   - Clinical seizure and EEG endpoints that may be used to guide adjustments to the tapering rate and/or cessation of the tapering attempt
   - Specific therapeutic escalation should seizures recur (e.g., whether to give additional intermittently dosed anticonvulsant medications, increase/resume the same continuous infusion, change to different continuous infusion, etc.)
5. The following tapering schedules are meant as a guide and should be individualized in the context of the above considerations:
   a. Midazolam – decrease 0.1 mg/kg/hour every 1-3 hours
   b. Pentobarbital – decrease 1 mg/kg/hour every 1-3 hours
   c. Ketamine – decrease 1 mg/kg/hour every 1-3 hours
   d. Propofol – decrease by 50% for 1-3 hours then discontinue.
6. While tapering continuous infusion agents, the EEG should be reviewed following each weaning step and before proceeding with the next step.
7. Good planning and clear communication of individualized patient care goals among all multidisciplinary team members, including bedside nursing, and with the patient's family, is critical during this process.

PARENT | CAREGIVER EDUCATION

Follow up

- A child who had a status epilepticus incident is at risk for experiencing status epilepticus again in the future.

- Discuss seizure first-aid and seizure precautions with the patient/family.
- Consider providing caregivers with the following handout: New Seizure Safety School Patient Station – English and Spanish
- Consider providing caregivers with the following handout: Home Therapy for Seizures: Using Intranasal Midazolam Therapy - English or Spanish.
- Consider providing caregivers with a Seizure Action Plan and a seizure rescue medication at the time of discharge.

RELATED DOCUMENTS

Propofol: Use in the Pediatric and Cardiac Intensive Care Units

Thermoregulation: Targeted Temperature Management PICU

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Pharmacy & Therapeutics Committee – May 2021
Clinical Pathways and Measures Review Committee – May 2021

MANUAL/DEPARTMENT	Clinical Pathways/Quality
ORIGINATION DATE	May 15, 2017
LAST DATE OF REVIEW OR REVISION	May 2021
COLORADO SPRINGS REVIEW BY	 Michael DiStefano, MD Chief Medical Officer, Colorado Springs
APPROVED BY	 Lalit Bajaj, MD, MPH Medical Director, Clinical Effectiveness

REVIEW REVISION SCHEDULE

Scheduled for full review on May 15, 2025

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