Status Epilepticus Management

INTRODUCTION

- Generalized convulsive status epilepticus (SE) is a serious and potentially life-threatening medical emergency that requires prompt intervention. Although the duration of seizures used to define status has varied over time, an accepted definition for the purposes of clinical practice defines SE as a single unremitting seizure lasting longer than five minutes or frequent clinical seizures without an interictal return to the baseline clinical state.

- **Status epilepticus (SE)** is considered one of the most common neurological emergencies with an estimated incidence of **20 cases/100,000 people** worldwide.

Facts

- The distribution is bimodal, peaking in patients **<1 and >60 years old.**
- In children, the cause is predominantly from febrile illnesses, with or without infection, and in adults it is largely secondary to acute damage from strokes or anoxic brain injuries.
- The **mortality rate is extremely high (30%** in adults and **3%** in children).
- Prognosis is largely affected by:
  - Etiology
  - Duration of seizure
  - Older age

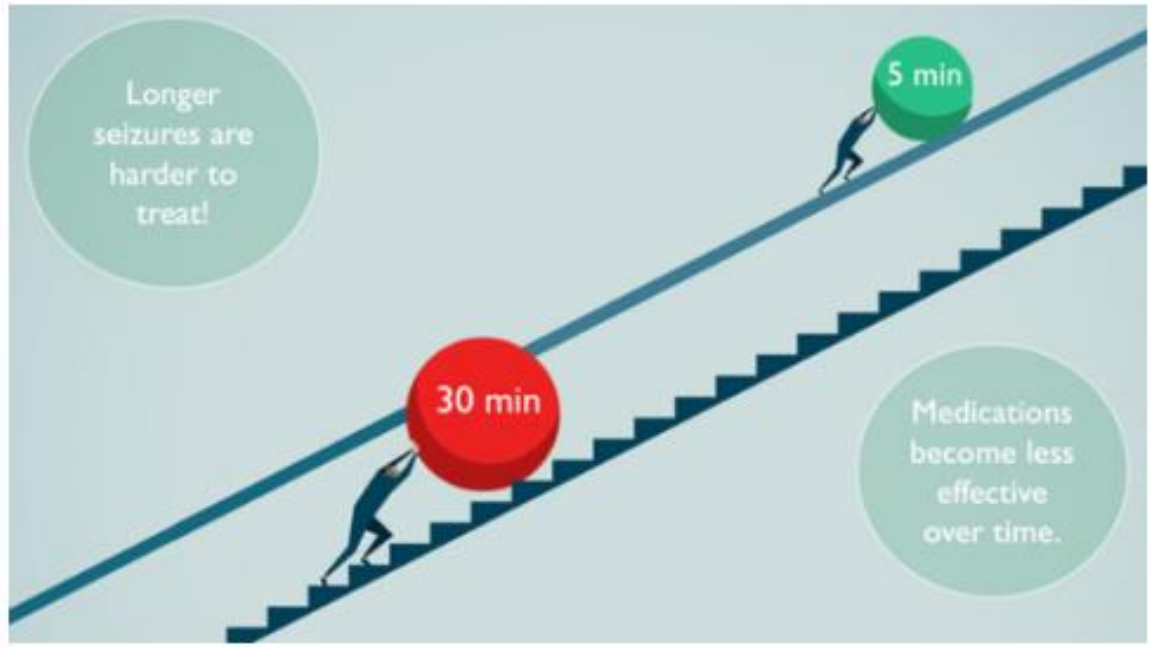
Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

- **Refractory SE**
- Defined as SE that is refractory to both 1st and 2nd line anti-epileptics. This is not to be confused with benzodiazepine-refractory SE, which as stated is only refractory to benzodiazepines.
- **Super-refractory SE**
- Defined as SE that is refractory to 1st, 2nd and 3rd line agents for 24 hours.

with time.



Delayed benzodiazepines = longer seizures and poorer outcomes

Benzodiazepine doses per current guidelines:

Drug dose			
Route	**Lorazepam**	**Midazolam**	**Diazepam**
IV	0.1 mg/kg (or 4 mg x2) *	--	0.15-0.2 mg/kg (or 5 mg x2) *
IM	--	0.2 mg/kg or 10 mg *	--
IN	--	0.2 mg/kg or 10 mg	--
Buccal	--	0.3 mg/kg or 10 mg	--
PR	--	--	0.2-0.5 mg/kg (or 10 mg x2)

* Preferred first line option

IM Midazolam if no IV
IV Lorazepam if IV obtained
If neither available, use Diazepam IV/PR or Midazolam IN/buccal

Drug	Avoid in the following conditions
Phenytoin	Intoxication, hypotension, known cardiac arrhythmias
Valproic acid	Liver disease, pregnancy
Levetiracetam	Mood disorders

IV anesthetics for treatment of refractory status epilepticus			
Drug	**Dose**	**Continuous infusion dose**	**Adverse effects**
Propofol	1-2 mg/kg IV	20-200 mcg/kg/min (increase rate by 5-10 mcg/kg/min q5 min, can repeat bolus)	Hypotension Respiratory depression Cardiac failure Rhabdomyolysis Propofol infusion syndrome
Midazolam	0.2 mg/kg IV	0.05-2 mg/kg/hr (increase rate by 0.05 - 0.1 mg/kg/hr q3-4h)	Respiratory depression Hypotension
Phenobarbital	20 mg/kg IV May give an additional 5–10 mg/kg	50–100 mg/min IV May give additional dose 10 min after loading infusion	Respiratory depression Hypotension Cardiac suppression Hypothermia Liver and pancreatic injury
Titrate to burst suppression on EEG.			

- ***Alternative routes of administration***

➢ Placement of an intravenous catheter may be difficult in some patients. If intravenous (IV) access is delayed or impossible, many antiseizure drugs can be given by alternative routes. Examples include buccal and intranasal midazolam, rectal diazepam, and intramuscular fosphenytoin and benzodiazepines, all of which are safe, well tolerated, and absorbed quickly.

➢ Many antiseizure medications can also be given via the intraosseous (IO) route if IV access is not available, including all benzodiazepines, phenytoin, and levetiracetam.

➢ However, if intravenous access is available, drugs administered by this route are more effective

RAPID EVALUATION

- Patients with generalized motor seizures that are frequent or separated by a period of significantly impaired consciousness or who are medically unstable require immediate assessment and treatment, which usually is accomplished in the setting of the emergency department.
- ***Initial assessment***

A brief physical examination should assess respiratory and circulatory status. An adequate airway should be established immediately if there is respiratory compromise, and supportive therapy (eg, oxygen, mechanical ventilation) should be instituted as needed. A secure intravenous catheter should be placed for sampling of blood and administration of medications. Ongoing monitoring of vital signs should be initiated.

A rapid neurologic examination should then be performed to provide a preliminary classification of the type of status epilepticus (SE). A history obtained from a parent or caregiver may help to determine the cause or precipitants of the seizures

- ***Laboratory studies*** — Blood and urine should be obtained for rapid determination of:

●Serum glucose and a rapid "finger-stick" glucose

●Serum electrolytes, calcium, and magnesium levels

●Arterial blood gases and pH

●A complete blood count

●Urine and blood toxicology

●Serum antiseizure drug levels

- An evidence-based review provided the strongest support for obtaining antiseizure drug levels; subtherapeutic levels are found in almost one-third of children presenting in SE
- Other testing in specific clinical circumstances may include

●Blood cultures and lumbar puncture (LP) should be obtained if there is evidence of systemic or central nervous system infection; there are insufficient data to support these tests being routine.

●Metabolic studies for inborn errors of metabolism should be considered if there are other suggestive indicators.

●Neuroimaging is generally deferred until the patient is stabilized. However, if LP is considered, computed tomography (CT) is generally recommended beforehand to exclude a mass lesion, especially in a patient with focal neurologic signs. Later, a magnetic resonance imaging study (MRI) is recommended if the etiology of SE is unknown.

Patient population	Studies
All patients	Serum electrolytes
	Serum calcium, phosphate, and magnesium
	Brain imaging (CT or MRI)*
	EEG
Epilepsy patients maintained on anticonvulsants	Anticonvulsant level
Febrile patients	CBC with differential
	Blood culture
	Urinalysis, urine culture
	CSF culture (once seizures stopped and if brain imaging excludes increased intracranial pressure)
Poisoned patient	Urine screen for cocaine, amphetamines, and PCP
	Aspirin level
	Venous or arterial pH and pCO_2
	EKG once seizures stop
Infants <6 months of age¶	Blood gas
	Plasma ammonia
	Plasma amino acids
	PT, PTT
	Serum AST, ALT, LDH, Alkaline phosphatase
	Blood lactate and pyruvate
	Urinalysis
	Urine for reducing substances
	Check newborn urine screening results if infant from country where instituted

- ***Monitoring***

Cardiac monitoring, frequent measurement of blood pressure, and pulse oximetry should be instituted. In general, SE does not independently cause systemic hypotension, although many of the drugs used to treat it do. The presence of low blood pressure should prompt consideration of an underlying systemic illness or infection.

- **Stabilization**

➢ Maintenance of an adequate airway and normal gas exchange

➢ Metabolic abnormalities should be corrected. Most children with acute seizures have elevated blood glucose levels that do not require treatment. However, nonketotic or ketotic hyperglycemia can occasionally precipitate SE and may be an early manifestation of diabetes

➢ Hypoglycemia should be treated with 2.5 mL/kg of 10 percent dextrose solution

➢ Metabolic acidosis often is present but usually resolves without treatment after the seizures are controlled. If the patient is febrile, antipyretics should be given.

- ***Electroencephalography***

➢ When there is uncertainty regarding the presence of SE, an urgent electroencephalogram (EEG) should be obtained. In the emergency department, this can be a limited study

➢ If an urgent EEG cannot be obtained, an EEG should be done to evaluate background activity as soon as possible after the seizure stops, ideally within one to two hours. The background usually remains abnormally slow for hours or even days after generalized convulsive or prolonged partial SE, but it is normal in psychogenic nonepileptic seizures unless large doses of sedating antiseizure drugs have been given. If the patient has not regained a relatively normal mental state within a few hours after SE has stopped, an EEG should be performed to evaluate the possibility of subclinical electrographic seizures

- ***Neuroimaging***

A neuroimaging study is essential when SE is the first presentation of epilepsy as well as in children whose recovery from SE does not follow the expected .Computed tomography may be performed in the emergency department setting, but magnetic resonance imaging has superior yield for determining the underlying etiology.

INITIAL TREATMENT

- **Immediate pharmacologic therapy**

SE should be treated immediately, as treatment delay is associated with increased morbidity and mortality

●**First therapy: Benzodiazepine** –

Lorazepam 0.1 mg/kg intravenously (IV) up to a maximum of 4 mg should be administered by slow IV push over one minute and its effect assessed over the next five to ten minutes

An equally effective alternative is **diazepam** 0.2 mg/kg IV (maximum dose 8 mg)

Treatment with benzodiazepine doses that are lower than recommended has been associated with a decreased likelihood of seizure cessation.If seizures continue after five minutes, additional doses of lorazepam or diazepam can be given

The risk of respiratory depression increases if more than two doses of benzodiazepines are administered

- **Second therapy: Antiseizure drug**

If seizures continue for 10 minutes after at least two injections of lorazepam or diazepam, a second therapy with a long-acting antiseizure drug is indicated

Some experts feel that phenytoin/fosphenytoin, levetiracetam, and valproate (VPA) are all equally reasonable choices in this setting .

- We begin treatment with levetiracetam 40 mg/kg IV, which we prefer over phenytoin because of ease of use, more rapid administration, and equivalent efficacy.
- Alternatively, fosphenytoin can be given at a dose of 20 mg phenytoin equivalents (PE)/kg IV and a rate of 3 mg PE/kg per minute (maximum rate 150 mg PE/min)
- If seizures persist, an additional 5 to 10 mg PE/kg IV of fosphenytoin can be given 10 minutes after the loading dose. Phenytoin and fosphenytoin may be less effective for the treatment of seizures due to toxins or drugs; in such cases, an alternative such as levetiracetam, VPA, or phenobarbital should be used
- Another option is to administer a weight-based dose of IV VPA or phenobarbital. VPA or phenobarbital may be used as initial therapy in children who did not respond to levetiracetam or fosphenytoin in previous episodes of SE, in children with a hypersensitivity to phenytoin, and in cases of toxin-induced SE. VPA may also be used as the initial treatment in children on chronic VPA therapy who are known to have had recent nonadherence and in whom VPA levels are suspected to be low.

- **Ongoing seizures despite first and second therapies**

In patients with ongoing seizure activity despite two initial doses of benzodiazepine and a second-therapy antiseizure drug, preparation for a continuous infusion of midazolam, propofol, or pentobarbital should occur simultaneously with administration of a different second-therapy antiseizure drug.

- **Antiseizure drugs (nonbenzodiazepine)**

Mounting evidence from randomized controlled trials and observational studies suggests that levetiracetam, fosphenytoin/phenytoin, and valproate have similar efficacy for convulsive status epilepticus in children.

- **When IV access is unavailable**

When IV and IO access cannot be achieved within the first three minutes, alternative first-line agents include]:

●Buccal midazolam 0.2 mg/kg, maximum 10 mg

●IM midazolam 0.2 mg/kg, maximum 10 mg

●Rectal diazepam 0.5 mg/kg, maximum 20 mg

Among these alternatives, buccal midazolam may be more effective than rectal diazepam

POSTICTAL RECOVERY

Most children begin to recover responsiveness within 20 to 30 minutes after generalized convulsions, although there is a broad range of duration

Close monitoring during this period is critical.

The two most common reasons for delayed postictal recovery are sedation from medications and ongoing nonconvulsive seizures .and these two causes can be impossible to distinguish clinically.

All children who do not return to a normal level of consciousness within a few hours after initial treatment of status epilepticus (SE) should therefore be monitored with electroencephalogram.

Secondary assessment

During the postictal recovery period it is also important to

- repeat a full neurological examination
- looking for asymmetric or focal findings that may suggest clues to the underlying etiology
- neuroimaging study should be obtained when SE is the first presentation of epilepsy as well as in children whose recovery from SE does not follow the expected course
- A lumbar puncture should be obtained if there is evidence of systemic or central nervous system infection, provided that the child's level of consciousness is appropriate and there are no other contraindications to immediate lumbar puncture.

REFRACTORY SEIZURES

- If convulsive status epilepticus (SE) persists for 30 minutes after initial measures are instituted (immediate benzodiazepine treatment followed by second therapy with an antiseizure drug), further pharmacologic therapy (third therapy) is required, usually in the form of continuous infusional therapy. The longer convulsive SE continues, the less convulsive it appears clinically, and continuous electroencephalogram (EEG) monitoring should be instituted.
- The three drugs most commonly used in this setting are pentobarbital, midazolam, and propofol. Among these, midazolam is the most frequent first-choice anesthetic agent, followed by pentobarbital .Although propofol has been used to treat SE, data are limited, and significant associated complications have been reported. It is contraindicated in the setting of ketogenic diet.

- **Midazolam**

- can be given as a continuous intravenous (IV) infusion for refractory SE and is associated with minimal cardiovascular side effects
- Midazolam is given as an initial bolus infusion of 0.2 mg/kg IV followed by a continuous infusion of 0.05 to 2 mg/kg/hour; for breakthrough seizures, additional 0.1 to 0.2 mg/kg boluses can be given and the continuous infusion rate increased by 0.05 to 0.1 mg/kg/hr every 3 to 4 hours

- **Pentobarbital**

- is given as an initial bolus infusion of 5 to 15 mg/kg IV followed by a continuous infusion of 0.5 to 5.0 mg/kg per hour
- Significant side effects include respiratory depression, hypotension, myocardial depression, and reduced cardiac output. Thus, intubation and mechanical ventilation with intravascular pressure monitoring are required prior to treatment, and inotropic agents frequently are needed. Other important potential complications include pulmonary edema, ileus, and prolonged sedation.

- **Propofol**

- IV anesthetic with rapid onset and short duration of action that is often used for elective procedures in children
- Side effects include hypotension, especially with rapid infusion . Other side effects include apnea and bradycardia. However, adverse cardiovascular effects occur less often with propofol than with pentobarbital. Hypertriglyceridemia and pulmonary edema may occur after prolonged use.
- Of significant concern is that maintenance infusions of propofol have been associated with fatal acidosis and rhabdomyolysis of the skeletal and cardiac muscles
- Others have found that propofol may be used without severe adverse effects if the dose is not titrated above 5 mg/kg per hour and with continuous monitoring and stopping the infusion if side effects appear
- Propofol should not be used in children on the ketogenic diet.

Other therapies

- **Lacosamide**

also available in both oral and intravenous formulations

The bolus dose most often used in adults is 200 to 400 mg IV infused over 3 to 5 minutes .Published data in children are limited [

- **Topiramate**

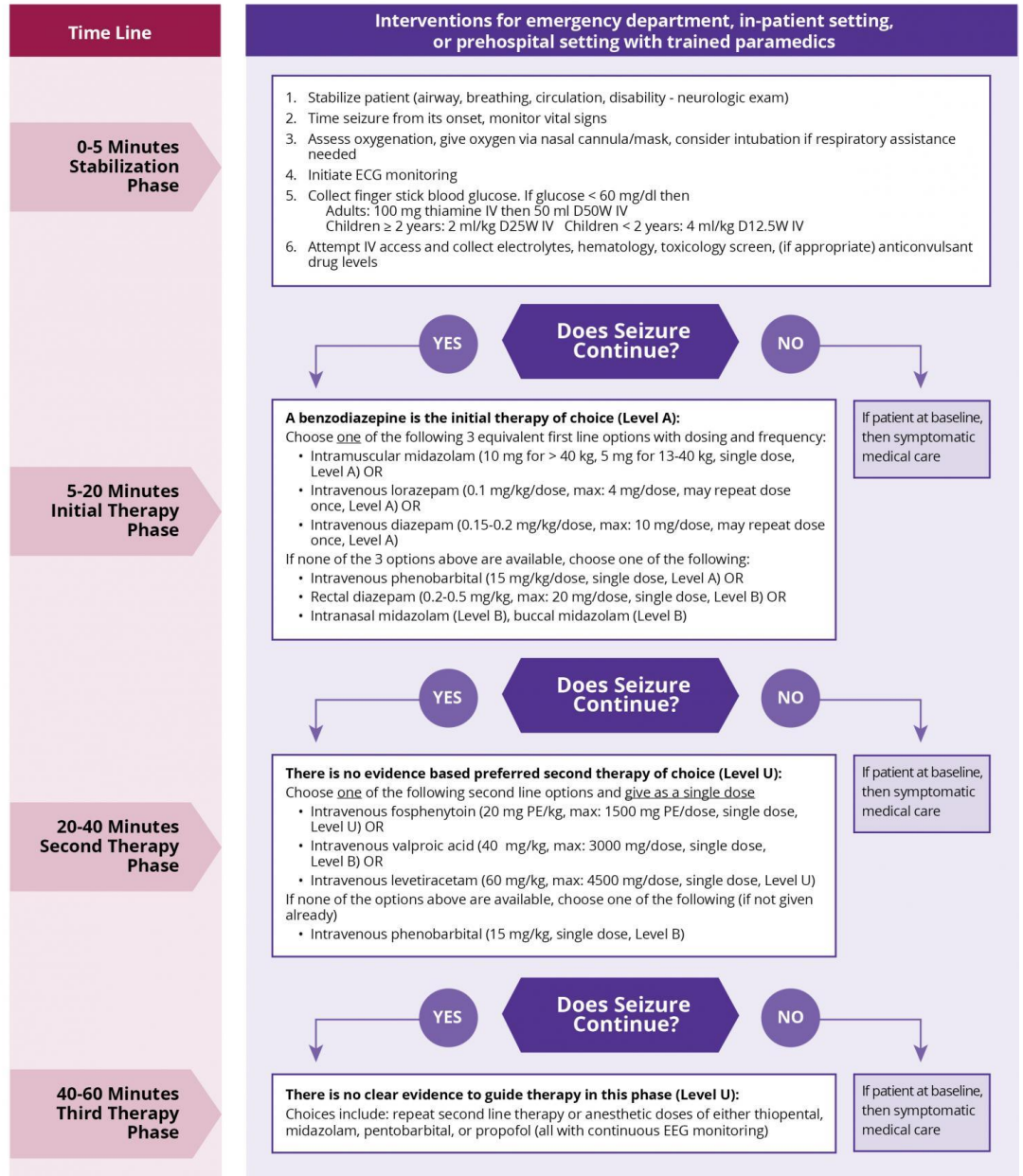
has a broad spectrum of efficacy against many seizure types. Case reports and small case series report that it may be efficacious in refractory SE .Some have used low initial doses [89,90], others a higher loading .There is no formulation for parenteral administration. Further prospective study is needed to define the role of topiramate in SE.

Duration of continuous infusions

Suppressive therapy with pentobarbital, midazolam, or propofol is generally used to induce a suppression-burst pattern on EEG for 24 to 48 hours. The dose is then slowly reduced to see if seizures reappear. If seizures are still present, the patient is placed back into suppression-bust for another 24 to 48 hours and then reassessed.

Proposed Algorithm for Convulsive Status Epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16.1 - Jan/Feb 2016



AMERICAN EPILEPSY SOCIETY

Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

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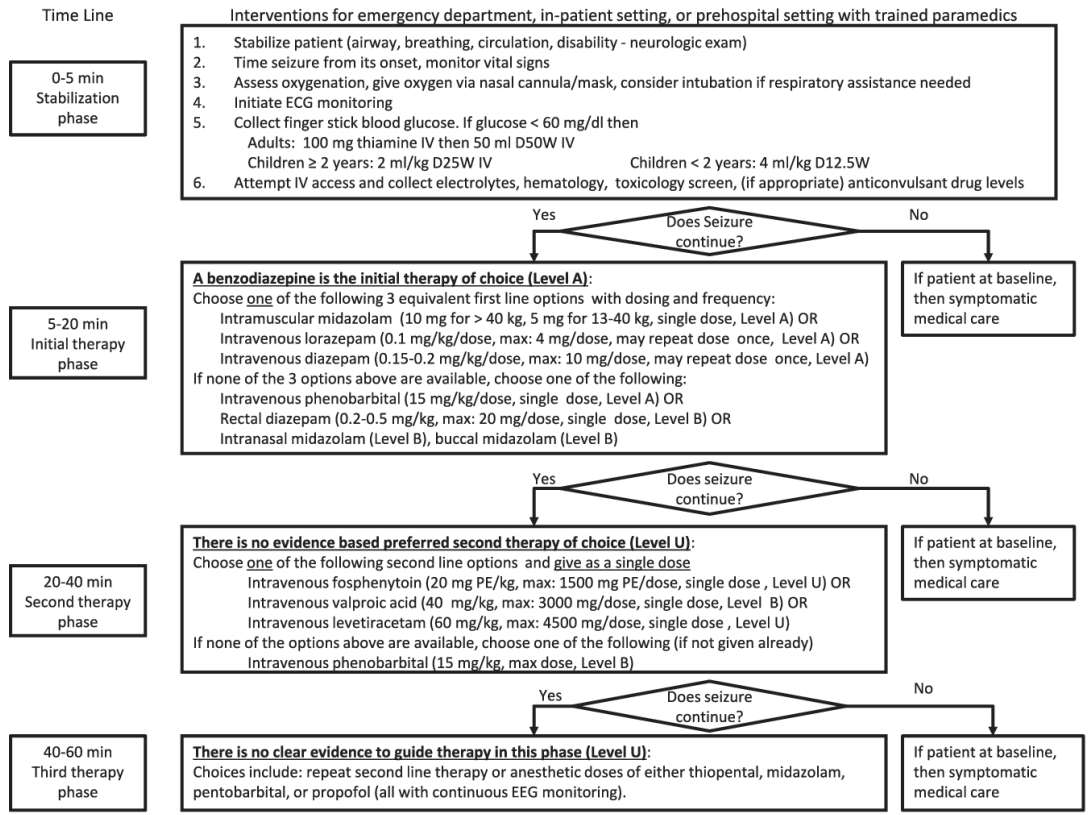

FIGURE 1. Proposed treatment algorithm for status epilepticus.

Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytical framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

In brief, as adapted from the AES guideline, there are 4 phases:

Stabilization phase (0-5 minutes)	ABC Timing of seizure from onset Finger stick glucose IV access + initial bloodwork (electrolytes and drug levels)
Initial therapy phase (5-10 minutes)	Choose one of the following (if available): • IV Lorazepam • IM Midazolam • IV Diazepam If these are not available, choose one of the following: • IV Phenobarbital • PR Diazepam • IN Midazolam
2nd therapy phase (20-40 minutes)	**There is no evidence to support a preferred agent.** Give a single dose of 1 of the following: • Fosphenytoin • Valproic acid • Levetiracetam If agents above are not available, give phenobarbital if not already given in the 1st phase.
3rd therapy phase (40-60 minutes)	**There is no clear evidence to guide therapy in this phase.** Choose from these options: • Repeat 2nd line therapy • Give anesthetic doses of thiopental, midazolam, pentobarbital or propofol.