SEIZURE- AND EPILEPSY-RELATED EMERGENCIES

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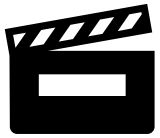
INTRODUCTION

- Seizures are a common cause of emergency medical evaluation, accounting for 1% of emergency department visits.
- Epidemiologic studies in the United States have shown that 11 % of the general population will have a seizure at some point in their life.
- Of these seizure patients, there is an estimated 1 million hospital visits due to seizures per year.



WHAT ARE POSSIBLE SCENARIOS?

- New onset seizures
- Breakthrough seizures in patients with known epilepsy
- Status epilepticus
- Acute adverse effects of antiepileptic drugs (AEDs)

STATUS EPILEPTICUS

- A scary medical emergency!
- Its incidence has seen an increase in recent years with 5 to 30 cases per 100,000.
- SE occurs at the extremes of life with an estimated annual incidence as high as 41 patients per year per 100,000 population.
- About one-third become refractory
- Mortality rate varies by etiology, clinical and electrographic features, and age, but ranges from 12–28%

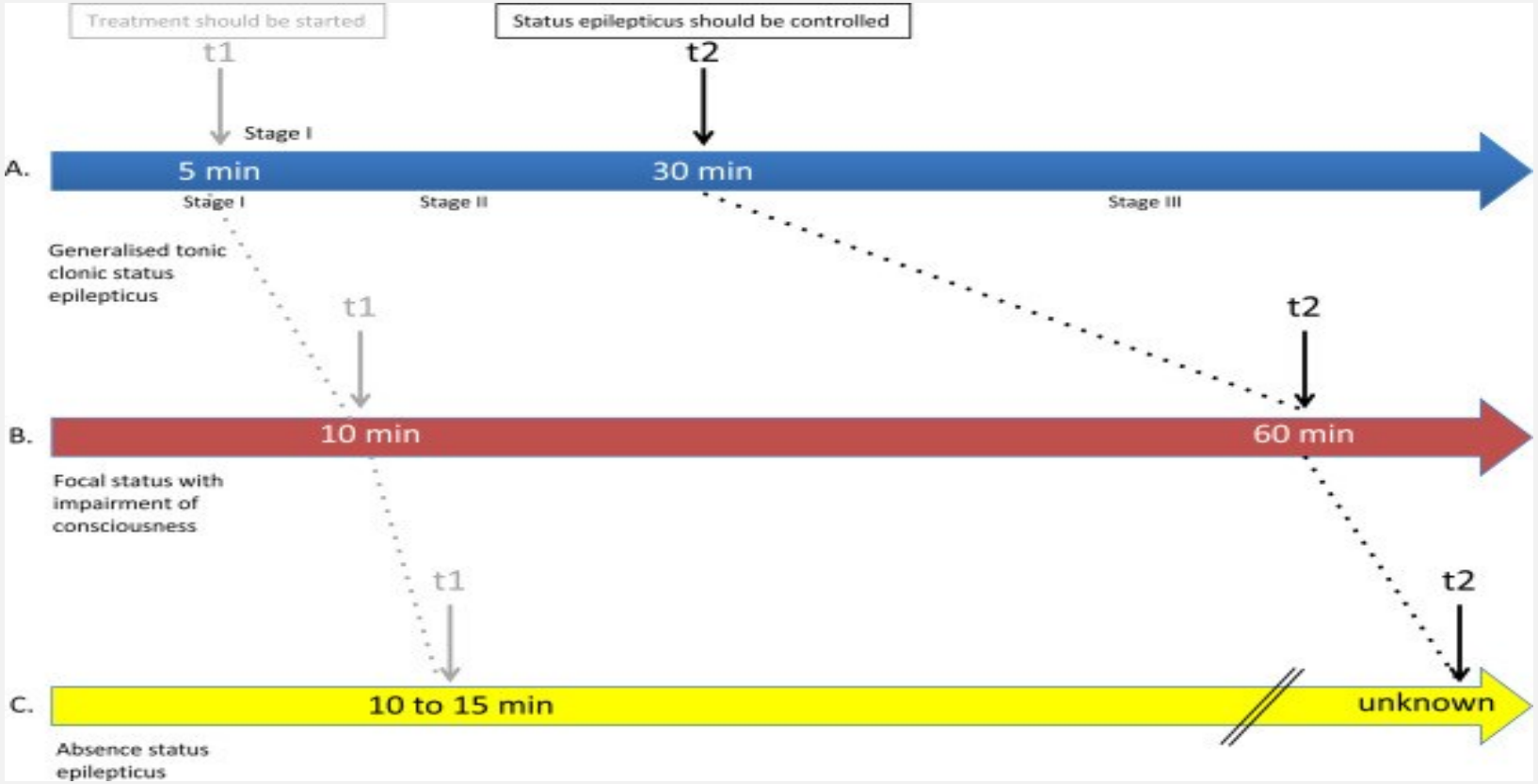
HOW IS SE DEFINED?

- Classic definition of SE: "an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epilepticus condition"
- As the need for a clinically applicable, operational definition, several attempts were made to be more precise by including a time duration
- Time varied from 30 minutes to 10 minutes and recently 5 minutes
- A "typical" self-limited generalized tonic–clonic seizure lasts 31 to 51 seconds, with a postictal phase of a few seconds to 4 minutes (overall 5 minutes)
- If the seizure duration was 5 to 10 minutes, it was unlikely to cease spontaneously within the next few minutes

NEW DEFINITION OF SE

- SE is seizure activity lasting 5 minutes or longer, or recurrent seizure activity without return to baseline in between seizures.
- Last ILAE definition included 2 times: t1 and t2
- T1 refers to the duration of seizure beyond which it is unlikely to terminate without intervention
- T2 refers to the duration of seizure beyond which long-term consequences occur.
- Therefore, in practical terms, t1 marks the point when emergency treatment for seizure termination needs to be initiated in order to prevent progression to time point t2

TIME LIMITS OF SE



GENERAL MANAGEMENT APPROACH OF SE

(a) Immediate termination of SE

(b) Managing underlying etiology

(c) Treatment of seizure-related complications

(d) Prevention of seizure recurrence.

IMMEDIATE TERMINATION OF SE

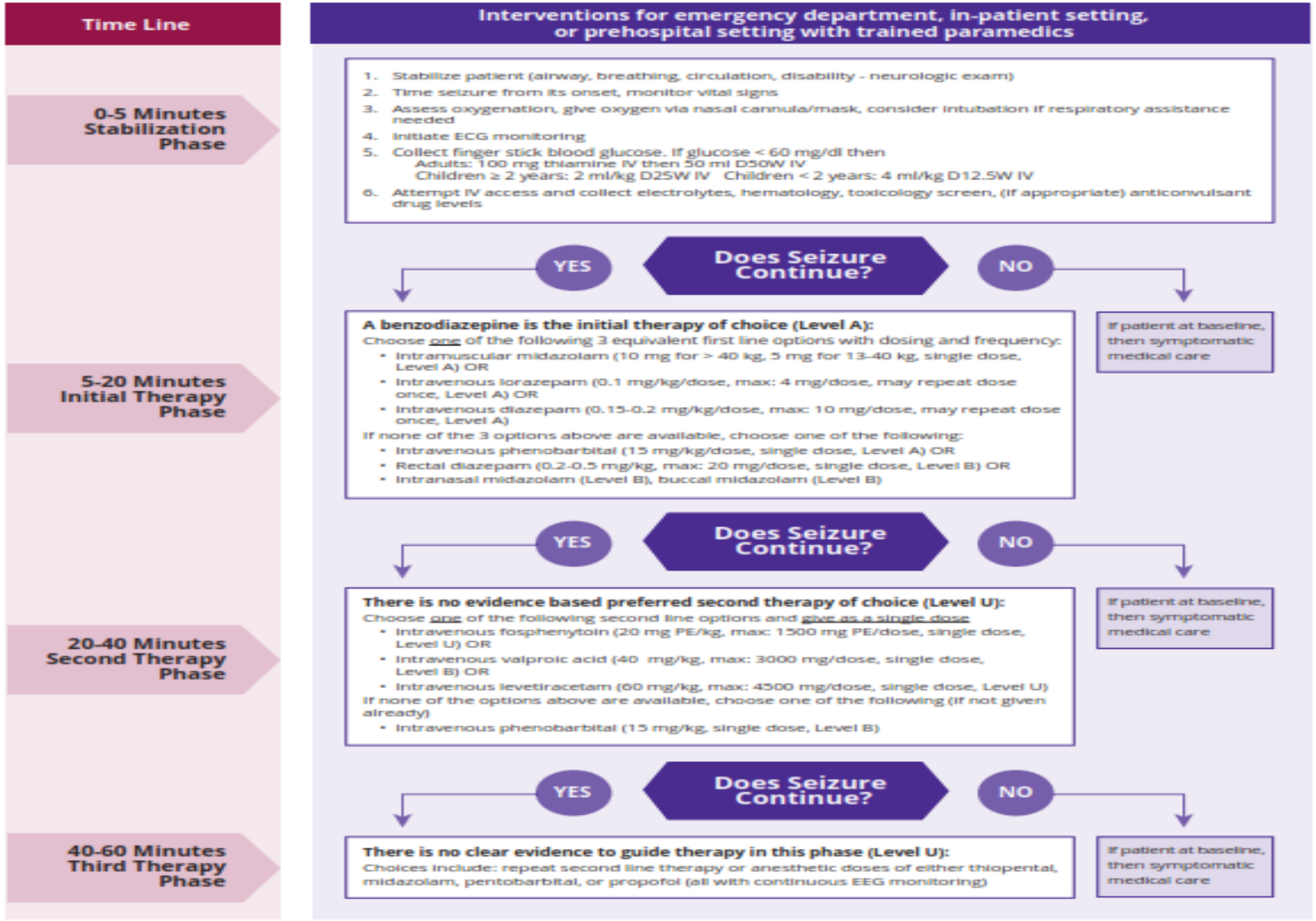
- The essential component of SE management is immediate seizure control
- Treatment should be aimed at controlling SE as soon as possible, particularly before brain compensatory mechanisms fail.
- Despite adequate oxygenation and ventilation, such failure has been noted within 30 to 60 minutes in experimental SE and within 30 to 45 minutes in humans

SE TERMINATION STEPS

- Stabilization phase (0 to 5 minutes)
- Initial therapy phase (5 to 20)
- Second therapy phase (20 to 40 minutes)
- Third therapy phase (40 to 60 minutes)

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.

0-5 MINUTES STABILIZATION PHASE

- ✓ Stabilize patient (airway, breathing, circulation, disability - neurologic exam)
- ✓ Time seizure from its onset, monitor vital signs
- ✓ Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed
- ✓ Initiate ECG monitoring
- ✓ Collect finger stick blood glucose. If glucose < 60 mg/dl then Adults: 100 mg thiamine IV then 50 ml D50W IV, Children ≥ 2 years: 2 ml/kg D25W IV, Children < 2 years: 4 ml/kg D12.5W IV
- ✓ Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug level

IMPORTANCE OF OXYGENATION AND CIRCULATION

- In the incipient or early stages of SE, brain compensatory mechanisms may protect against neuronal injury.
- However, at t in the new ILAE definition of SE, the ability to compensate for neuronal injury is exhausted, and the risk of neuronal injury increases.
- During all stages, the ability to compensate requires adequate airway and good breathing, circulation, and cerebral blood flow.
- Decreases in brain parenchymal oxygenation, cerebral blood flow, and brain glucose all contribute to an energy mismatch.

5-20 MINUTES INITIAL THERAPY PHASE

- ✓ A benzodiazepine is the initial therapy of choice : Choose one of the following 3 equivalent first line options with dosing and frequency:
  - Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose)
  - Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once)
  - Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once)

5-20 MINUTES INITIAL THERAPY PHASE

- ✓ If none of the 3 options above are available, choose one of the following:
  - Intravenous phenobarbital (15 mg/kg/dose, single dose)
  - Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose)
  - Intranasal/buccal midazolam

20-40 MINUTES SECOND THERAPY PHASE

- ✓ There is no evidence based preferred second therapy of choice: Choose one of the following second line options and give as a single dose
  - ➢ Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose)
  - ➢ Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose)
  - ➢ Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose)
- ✓ If none of the options above are available, choose one of the following (if not given already)
  - ➢ Intravenous phenobarbital (15 mg/kg, single dose)

PHENYTOIN

- IV loading dose in normal saline (it precipitates with dextrose) at 20 mg/kg (15 mg/kg in the elderly)
- No respiratory depression or sedation
- Infusion rate no faster than 1 mg/kg/min in a child (not to exceed 25 mg/minute), 50 mg/minute in an adult, and 20 mg/minute in the elderly
- Avoid rapid infusion , as may cause hypotension or arrhythmias.
- Pulse and blood pressure should be monitored, decrease infusion rate if hypotension develops
- IV PHT has an alkaline pH and contains solvents that can cause vascular irritation, cardiac depression, and hypotension.

FOSPHENYTOIN

- The phosphate ester prodrug of phenytoin
- Dosed as phenytoin equivalents (PE) at 20 mg PE/kg, 150 mg/min
- Can be administered in a dextrose solution
- Water soluble and may be given by the IM route
- Favorable side effect profile (including cardiovascular, phlebitis,…)
- Has replaced phenytoin in SE treatment guidelines

VALPROIC ACID

- 40 mg/kg at a rate of 20 to 50 mg/minute
- Good cardiovascular and respiratory tolerability
- Despite preference for phenytoin use, IV valproic acid may be of equal efficacy without the caveats of phenytoin's side effects.
- A good initial choice for second-line medication in the treatment of benzodiazepine-resistant SE and has a good side effect profile
- Consider interaction with penem antibiotics for maintenance use

LEVETIRACETAM

- 60 mg/kg 2 to 5 mg/kg/min IV
- Pharmacokinetic profile is similar for IV and oral LEV
- Favorable safety profile
- No significant drug interactions

PHENOBARBITAL

- Has been used in all age groups
- Primarily relegated to the second line but continues to be used as a first-line agent in the treatment of SE in the neonate
- Respiratory depression and sedation occur
- 15 to 20 mg/kg, administered at a rate no higher than 100 mg/minute in older children and adults and 20 mg/kg in neonates and infants.

BEST TIME FOR SECOND-LINES

- Second-line therapy administration should ideally occur concomitantly with first- line benzodiazepine therapy
- Benzodiazepine therapy alone has a short duration of treatment effect and will not be effective in preventing prolonged seizures or SE.
- There is no need to delay the administration of second-line therapy to assess if the patient responds to first-line benzodiazepine therapy.

40-60 MINUTES THIRD THERAPY PHASE

- There is no clear evidence to guide therapy in this phase, choices include:
  - Repeat second line therapy
  - Anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol, ketamine (all with continuous EEG monitoring)

WHICH OPTION?

- Some experts advocate for more aggressive treatment of SE (rapid sequence termination of SE)
- Rather than treating with second-line AEDs, waiting for a clinical response, and reloading with these agents, the idea of proceeding directly to continuous IV agents while concomitantly using second-line AEDs have been proposed.
- If convulsive activity has stopped but mental status does not improve, NCS or NCSE must be excluded. The prevalence of repetitive NCS in this situation may be as high as 48%
- Continuous EEG monitoring required to reach burst-suppression and maintain it for at least 24-48 hours

EARLY ANESTHETIC THERAPY

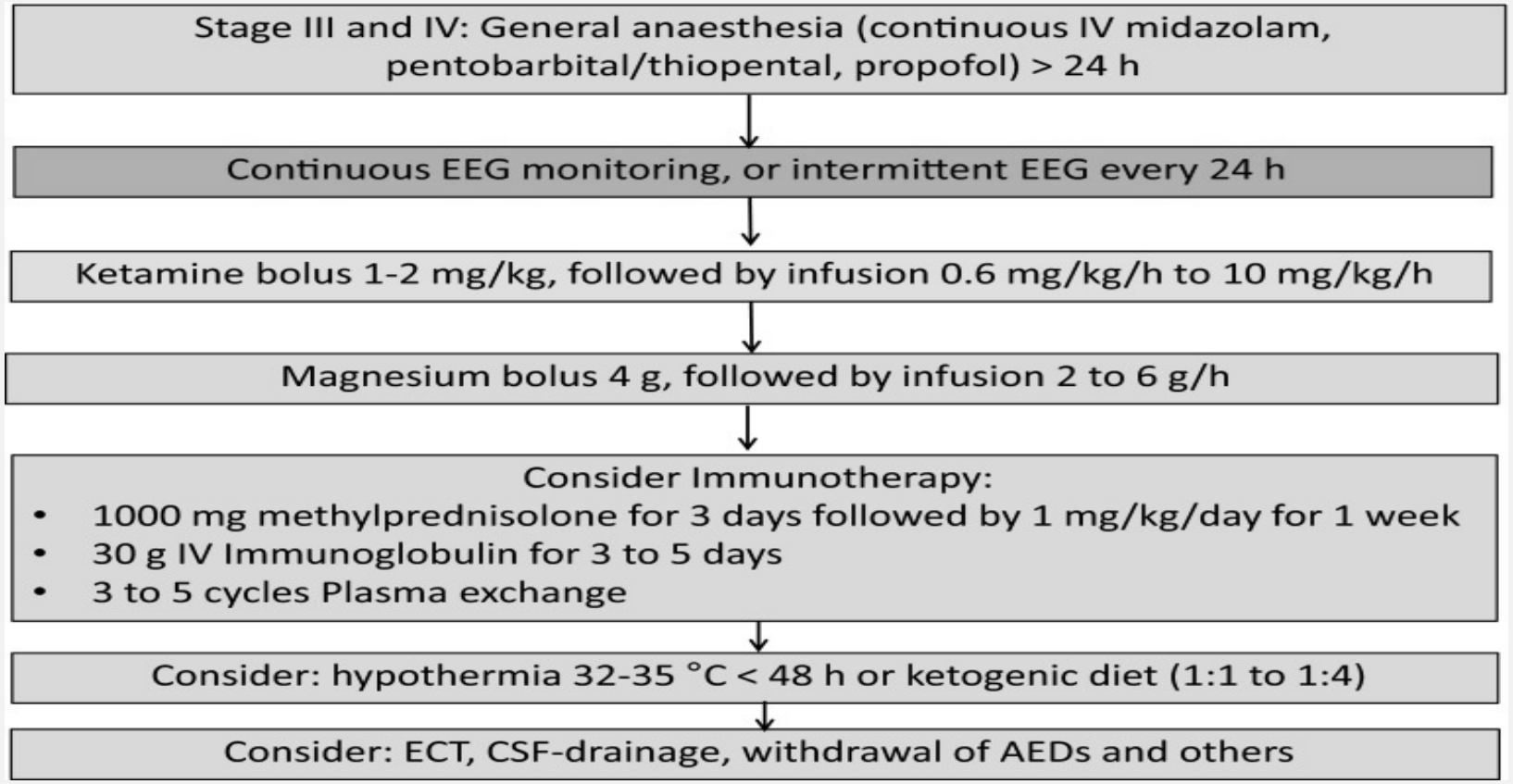
- Postoperative patients, especially cardiac surgery and neurosurgery
- Brain tumor, head trauma, increased intracranial pressure, intracranial hematoma, subarachnoid hemorrhage
- Stroke: ischemic, hemorrhagic
- CNS infections (meningitis, encephalitis, brain abscess)
- Organ failure, especially hepatic or multisystem failure
- Hyperthermia, malignant hyperthermia, hyperthyroidism
- Metabolic disorders prone to increased intracranial pressure, diabetic ketoacidosis, or organic acid disorders

	Bolus	Infusion	Special considerations
Midazolam	0.2 mg/kg q5min,max 2 mg/kg	0.1–2.9 mg/kg/h	Tachyphylaxis
Propofol	2 mg/kg q5min; max 10 mg/kg	30-200 μg/kg/min	Avoid use≥80μg/kg/min for ≥48h, adjust daily calorie intake by 1.1 kcal/mL, propofol syndrome!
Pentobarbital	5 mg/kg q5min, max15 mg/kg	0.5–5 mg/kg/h	
Ketamin	1–2 mg/kg q5min;max4.5 mg/kg	1.2–7.5 mg/kg/h	Supraventricular tachycardia, bradyarrhythmias
Thiopental	2–7 mg/kg up to 50 mg/min	0.5–5 mg/kg/h	Metabolized to pentobarbital

4 STAGES BASED ON SE RESPONSIVENESS TO AED

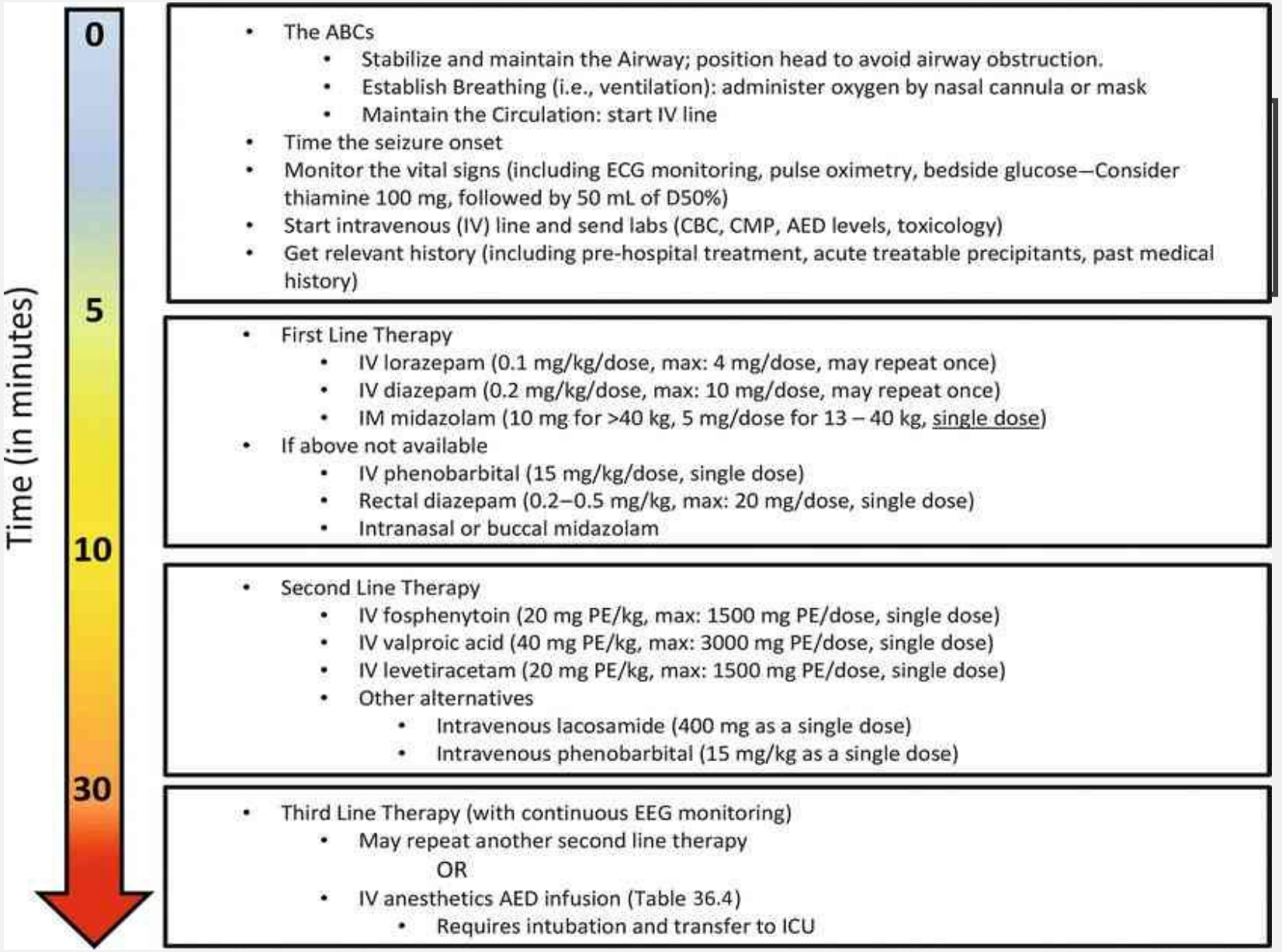
- Early or emerging SE
- Established SE (ESE): seizure persisted despite appropriate first-line treatment
- Refractory SE (RSE): seizure continued despite the use of a second-line agent
- Super refractory SE (SRSE): when an episode of RSE does not respond to IV anesthetics

AN EXAMPLE PROTOCOL FOR SRSE



MORE RECENT SE ALGORITHM

- As SE is a battle against time, a more time-sensitive SE treatment protocol, modified from AES guidelines, is presented
- History has been noted
- Lacosamide


Time (in minutes)
0
5
10
30
The ABCs
Stabilize and maintain the Airway; position head to avoid airway obstruction.
Establish Breathing (i.e., ventilation): administer oxygen by nasal cannula or mask
Maintain the Circulation: start IV line
Time the seizure onset
Monitor the vital signs (including ECG monitoring, pulse oximetry, bedside glucose—Consider thiamine 100 mg, followed by 50 mL of D50%)
Start intravenous (IV) line and send labs (CBC, CMP, AED levels, toxicology)
Get relevant history (including pre-hospital treatment, acute treatable precipitants, past medical history)
First Line Therapy
IV lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat once)
IV diazepam (0.2 mg/kg/dose, max: 10 mg/dose, may repeat once)
IM midazolam (10 mg for >40 kg, 5 mg/dose for 13 – 40 kg, single dose)
If above not available
IV phenobarbital (15 mg/kg/dose, single dose)
Rectal diazepam (0.2–0.5 mg/kg, max: 20 mg/dose, single dose)
Intranasal or buccal midazolam
Second Line Therapy
IV fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose)
IV valproic acid (40 mg PE/kg, max: 3000 mg PE/dose, single dose)
IV levetiracetam (20 mg PE/kg, max: 1500 mg PE/dose, single dose)
Other alternatives
Intravenous lacosamide (400 mg as a single dose)
Intravenous phenobarbital (15 mg/kg as a single dose)
Third Line Therapy (with continuous EEG monitoring)
May repeat another second line therapy
OR
IV anesthetics AED infusion (Table 36.4)
Requires intubation and transfer to ICU

LACOSAMIDE

- Approved by the U.S. FDA in 2008 for adjunctive therapy for focal-onset seizures in patients 17 years of age and older.
- IV formulations also available and have been used in SE
- Loading dose of 400 mg

GENERAL MANAGEMENT APPROACH OF SE

(a) Immediate termination of SE

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F0CUSED HISTORY

- What symptoms were seen?
- Hemibody versus generalized activity
- What time was patient last seen normal?
- How long did the activity last?
- Did the patient return to baseline at any point?
- Medication use
- Recent illness or fever
- Preceding trauma
- Prior medical history (e .g., stroke, brain tumor, brain infection)

RED FLAGS FOR LIFE-THREATENING CAUSES OF SEIZURES

- Meningitis: Nuchal rigidity, fever, rash
- Transtentorial herniation: Anisocoria
- Hemispheric lesions: Gaze deviation, hemiparesis
- Trauma: Periorbital ecchymosis

WORK-UP FOR UNDERLYING ETIOLOGY

- Call for initial lab results (electrolytes, toxicology,…)
- Consider LP if indicated
- Consider imaging (emergent brain CT, then MRI for further evaluation)
- Look for autoimmune/vasculitis etiologies

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Cardiac	Hypertension, tachycardia (reversing after 30 minutes), arrhythmias, cardiac arrest
Pulmonary	Apnea, respiratory failure, hypoxia, neurogenic pulmonary edema, aspiration pneumonia
Autonomic	Fever, sweating, hypersecretion (including tracheobronchial), vomiting
Metabolic	Hyperkalemia, hyperglycemia then hypoglycemia, volume depletion, venous stasis, possible thrombosis
Cerebral	Cerebral edema, raised intracranial pressure, Cortical vein thrombosis
Other	Leukocytosis, cerebrospinal fluid pleocytosis, vertebral and other fractures, physical injury, rhabdomyolysis, renal failure, disseminated intravascular coagulation

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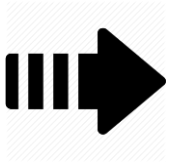


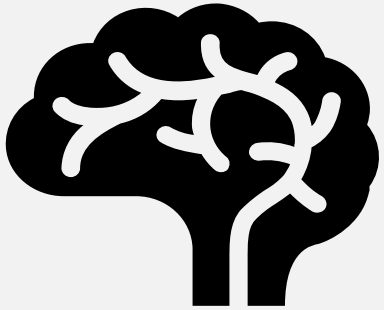
MAINTANANCE ANTIEPILEPTIC DRUGS

- Send AED levels 2 hours after loading
- Start maintenance AEDs at least 6 hours after loading
- Optimize patient's maintenance AED agents (therapeutic or even supratherapeutic level), so reasonable to administer near full dose then taper
- Usual doses: Levetiractam 1g/TDS, Valproic acid 800mg/TDS, Phenytoin 100/TDS
- Oral drugs possible to add if NG tube fixed

BE PREPARED

- Update your knowledge regularly
- Order necessary drugs in advance

BE FAST! TIME IS BRAIN…



BE BRAVE! YOU WILL BE DEFEATED IF NOT AGGRESSIVE ENOUGH…

ANY QUESTIONS?

NEW ONSET SEIZURES

STEP 1: WAS IT TRULY A SEIZURE?!

- Positive symptoms such as paresthesias, limb jerking, olfactory or auditory phenomena, experiential symptoms such as déjà vu
- Confusion following the event
- Tongue biting
- Urinary incontinence

RULE OUT SEIZURE MIMICS

- A prodrome of lightheadedness, nausea, and clamminess, followed by immediate return to baseline upon awakening, suggests syncope Importantly, convulsive jerking can occur during syncopal episodes, and incontinence or mild tongue biting can also occur
- Strokes and transient ischemic attacks are usually characterized by negative symptoms, such as weakness or vision loss
- Migraines typically include a headache, although some migraines are painless and include a visual aura that can be mistaken for a seizure aura.

RULE OUT SEIZURE MIMICS

- Psychogenic nonepileptic seizures often include preserved awareness, asynchronous or nonrhythmic limb movements, side-to side head shaking, ictal stuttering, grimacing, pelvic thrusting, or forced eye closure
- Remains a diagnosis of exclusion and should be verified with video electrocephalographic (EEG) monitoring

STEP 2: ARE THERE ANY PROVOCATIVE FACTORS?

- Alcohol withdrawal
- Hypo/hyperglycemia
- Electrolyte disturbances (Na, Ca, Mg),
- Amphetamine, cocaine, and opiate intoxication
- Benzodiazepine withdrawal
- LP if CNS infection suspected

STEP 3: IS THERE ANY ETIOLOGY IN THE CNS?

- If unprovoked, neuroimaging and an EEG to look for an etiology and to decide whether to initiate treatment with an AED.
- A brain CT in the emergency department to rule out a hemorrhage or other lesion requiring immediate treatment.
- Brain MRI in the ED/outpatient, 23% of patients with new onset seizures having a lesion on MRI
- EEG as soon as possible ideally within 12 hours of the event

STEP 4: DOES IT NEED AN ANTIEPILEPTIC DRUG?

- Epilepsy needs an antiepileptic drug!
- Epilepsy definitions:
- 1. Older: two unprovoked seizures, so have a careful history to ensure there was not a prior unrecognized seizure (such as unexplained nocturnal incontinence or bruising) or signs indicative of epilepsy syndromes (myoclonus,…)
- 2. New: a first unprovoked seizure with a 60% or greater chance of a second unprovoked seizure within the next 10 years, in practice, patients with a prior brain injury, abnormal neuroimaging or EEG findings, or nocturnal seizures
- Treatment can be started in the ED or outpatient

BREAKTHROUGH SEIZURES

LOOK FOR SEIZURE TRIGGERS AND TREAT ACCORDINGLY

- Missed or delayed AED doses;
- Recent fevers or infectious symptoms particularly vomiting or diarrhea, as these may affect medication absorption;
- Recent changes in medication dosing or new medications, including non-AED medications
- Sleep deprivation or other physiologic or emotional stressors

INVESTIGATIONS

- Basic laboratory studies(basic metabolic panel, complete blood count, and liver function tests) often ordered but rarely abnormal
- Perform a brain CT if:
  - ✓ an atypical seizure(not resolving within 3 to 5 minutes without intervention)
  - ✓ head trauma during the seizure,
  - ✓ have an abnormal neurological exam after the seizure
  - ✓ immunocompromised
  - ✓ taking anticoagulant or antiplatelet medications
  - ✓ have a known intracranial lesion
- AED serum levels

ACUTE ADVERSE EFFECTS OF ANTIEPILEPTIC DRUGS (AEDS)

ACUTE PEAK DOSE CENTRAL NERVOUS SYSTEM EFFECTS OF ANTIEPILEPTIC DRUGS

- Symptoms: Dizziness, diplopia, ataxia, vision changes, and lethargy
- Are reversible
- Have been reported with nearly all of the available AEDs
- Typically occur between 20 minutes and 1 hour after dose administration, when the serum level peaks
- Can also occur with a compliant patient on a steady dose if changes in other medications change the AED's metabolism(most often, removal of an enzyme-inducing agent will result in increasing AED levels over several weeks)

OTHER EMERGENT ADVERSE EFFECTS

- Kidney stones associated with Topiramate and Zonisamide use
- Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis classically associated with lamotrigine, but also with phenytoin, carbamazepine, phenobarbital (best alternatives: valproic acid, levetiracetam)
- Hyponatremia associated with Carbamazepine and Oxcarbazepine use, significantly associated with AED levels
- Hyperammonemia associated with Valproic Acid

ANY QUESTIONS?