MANAGEMENT OF STATUS EPILEPTICUS

Vahid Salehifar

Neurologist, Epileptologist

Introduction

- The management of status epilepticus and its pharmacological treatment still represents an area with **limited evidence** derived from high-quality, adequately powered randomized controlled trials (RCTs) to inform clinical practise.
- However, there have been clear advances in the understanding of the pathomechanisms, which have led to more effective treatment strategies.
- The therapeutic principle "time is brain" applies **not only for stroke but also for status epilepticus**, as the prognosis of SE worsens with increasing duration of seizure activity.
- The cost of status in the refractory stages are high and a recent study in Germany has estimated s1,365/day.

The general management approach of patients with SE

(a) Immediate termination of SE

(b) Managing underlying etiology

(c) Treatment of seizure-related complications

(d) Prevention of seizure recurrence

Diagnostic studies

- The **initial management** begins with the basics of emergency treatment **ABCs** —airway, breathing, and circulation.
- **Diagnostic studies** are then selected, depending on a patient's history and physical examination (not all studies need to be obtained for every patient).
- **Serum glucose** should be checked immediately with bedside glucose testing to rapidly rule out hypoglycemia as a cause of SE.
- A **complete blood count** may be helpful for diagnosing infection, although leukocytosis may occur with SE in up to 60% of patients with counts ranging from 12,700 to 28,800 cells/mm^3 .

Diagnostic studies

- Electrolytes, calcium, phosphorous, and magnesium values may also be helpful.
- **Lumbar puncture** (LP) should be considered in the febrile patient, although cerebrospinal fluid (CSF) pleocytosis may occur without infection, presumably due to a breakdown in the blood–brain barrier.
- Along with peripheral and CSF pleocytosis, hyperthermia is also commonly noted in SE, especially GCSE.
- However, these changes are transient and typically reversible in 24 hours after the ictal event.
- If there is concern about increased intracranial pressure or a structural lesion, LP can be deferred until neuroimaging is performed.
- If there is evidence of infection, antibiotics can be administered prior to LP.
- In those taking an antiseizure medication (**ASM**), levels should be obtained as low ASM levels may contribute to the development of SE.

Neuroimaging

- Neuroimaging options include CT scan and MRI.
- **CT scans** are readily available on an emergency basis and has the potential to identify disorders demanding immediate intervention, such as tumor, hemorrhage, or hydrocephalus (note: stroke in its early stage may not be seen by a CT scan).
- CT scan and MRI may detect focal changes, which may be transient, secondary to a focal seizure (suggesting the origin of the focus), with MRI being the more sensitive technique.
- Although these lesions may mimic those of **ischemic stroke**, they are known to cross vascular territories.
- Changes in diffusion-weighted images and the apparent diffusion coefficient suggest both cytotoxic and vasogenic edema.
- Progressive changes also occur, such as **hippocampal atrophy** and **sclerosis** or **global atrophy**.

Neuroimaging

- In the **FEBSTAT** study, a prospective study of children between 1 month and 5 years of age who experienced an episode of febrile SE, **9% (17/191)** were found to have increased T2 signal in the hippocampus, maximum in Sommer sector, when imaging was completed within 72 hours of presentation, and another approximately **2.5% (5/191)** had an equivocal finding.
- None of the 96 children with a first simple febrile seizure who made up the control group were found to have a similar increase in signal .
- Repeat imaging in this cohort obtained approximately **1 year later** demonstrated retarded hippocampal growth after febrile SE and, in several of the children with acute findings, the development of imaging characteristics of **hippocampal sclerosis.**
- A recent study looked at patients who underwent MRI within 30 days from the beginning of SE, which were reviewed by two independent investigators.
- Among 277 patients analyzed, 32 (12%) showed peri-ictal MRI abnormalities, which were highly correlated with duration of SE and focal EEG findings, specifically *lateralized periodic discharges* .

Neuroimaging

- Neuroimaging should be performed in all patients with new-onset SE, especially if there is no prior history of epilepsy.
- Functional neuroimaging like PET scan and whole-body imaging may be indicated as well in new-onset refractory SE (NORSE) cases.

EEG

- An EEG is not immediately needed for treatment.
- Indications for emergency EEG include **unexplained altered awareness** (to exclude NCSE), the use of **neuromuscular paralysis** in a patient with SE, **high-dose suppressive therapy** for refractory SE, and **no return to baseline or improvement in mental status** following control of overt convulsive movements (to exclude ongoing subtle SE).
- A recent expert consensus recommendation by the critical care cEEG task force of the ACNS for the use of cEEG in critically ill adults and children found the incidence of **NCSE to be as high as 48% in adults** and even higher proportion of children depending on the setting of cEEG and the underlying etiology.
- EMS called for out-of-hospital SE may not able to diagnose 15% patients with convulsive SE, all of whom, in a study, had a transformation to subtle or NCSE.
- Therefore, there should be a low threshold for the use of EEG in such cases or in situations when the diagnosis is in doubt, especially where there is concern for pseudoseizures.

ASM for the Treatment of Status Epilepticus

- Treatment should be aimed at **controlling SE as soon as possible**, particularly before brain compensatory mechanisms fail.
- **Neuron- specific enolase**, a marker of brain injury, is elevated in the serum following both convulsive and NCSE in humans.
- Many of the ASMs used to treat SE have the potential for respiratory and cardiac depression, especially when administered by a **loading dose** or when an **excessive dose** is used.
- Therefore, protecting the airway, controlling ventilation, and monitoring cardiac and hemodynamic function are mandatory.
- However, there is also some evidence to suggest that the rate of these complications is substantially higher in untreated SE compared to patients treated with intravenous (IV) benzodiazepines.

ASM for the Treatment of Status Epilepticus

- IV administration is the preferred route for the treatment of SE, especially in the inpatient setting, but if IV access is difficult, intramuscular (IM), rectal, or intranasal routes have been used.
- ASM management, depending on the **rapidity of its administration**, **underlying etiology**, and still **poorly understood mechanisms**, may have variable impact on SE abortion.
- SE is a dynamic syndrome.
- Proposed methods for staging SE have included **EEG**, **duration**, and **response to treatment.**

ASM for the Treatment of Status Epilepticus

- An episode of SE can be divided into 4 stages based on its ASM responsiveness and the escalating therapeutic management used:
  - Emerging SE
  - Established SE (ESE)
  - Refractory SE (RSE)
  - Super-refractory SE (SRSE)
- **ESE** denotes a prolonged seizure that has persisted despite appropriate first-line treatment.
- Prior to this point, SE can be referred to as early or **emerging**.
- Once established, **a** second- line ASM , which is traditionally a nonsedating IV ASM, should be initiated.
- If the seizure continues despite the use of **a** second-line agent, there are data to suggest that the third ASM agent is substantially less effective than first agent in aborting seizure and at that point, the episode of SE can be considered **refractory** (refractory SE or RSE).
- The last stage of **SRSE** is reached when an episode of RSE does not respond to IV anesthetics.

ASM for the Treatment of Status Epilepticus

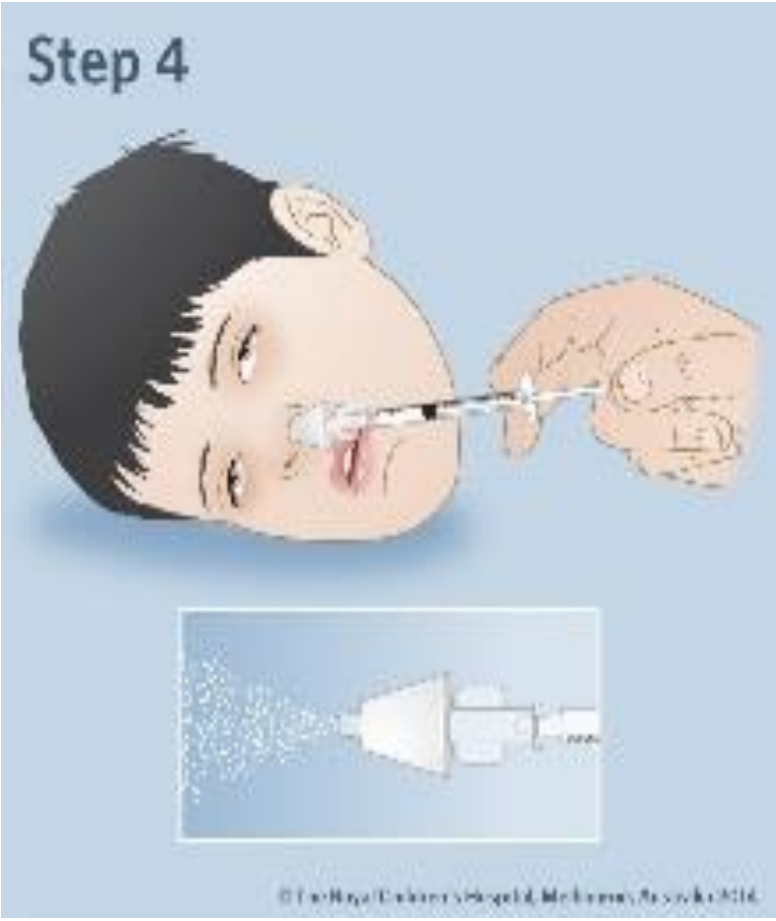
- The early treatment regimen of SE has evolved and matured over time.
- Today, we have some ASMs with clear, **class I evidence** for their use as first- line agents for seizure termination in SE.
- In contrast, there are ASMs that are typically used as second- and third-line agents in the absence of definitive evidence to support their efficacy.

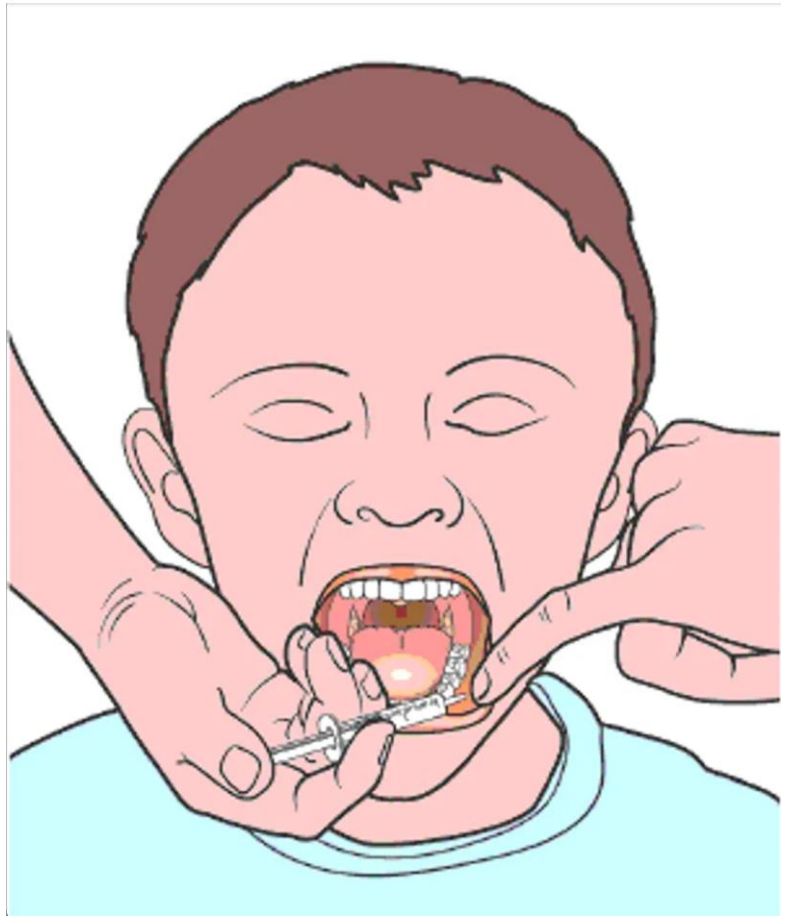
Prehospital Treatment

- The advent of *per rectum* administered ASMs permits the premonitory or early stage to be treated prior to hospital arrival by the **caregiver or family** even prior to EMS arrival, although other routes of administration are also used.
- **Rectal diazepam** can be administered at home for the treatment of SE or serial seizures; the maximum dose is 20 mg.
- **A rectal gel** preparation is available, which is easier to administer.
- Although only approved by the U.S. FDA for the treatment of selected, refractory patients on stable regimens of ASMs for the treatment of seizure exacerbation, the **rectal gel** is used as a therapeutic remedy for SE at home.
- However, recent studies have shown its underutilization by families.

Prehospital Treatment

- **Lorazepam** can be administered sublingually, and **midazolam** can be given by intranasal or buccal mucosa routes, with rapid buccal absorption.
- These are more socially acceptable and presumed to be more convenient alternatives to rectal diazepam for the treatment of SE.
- One study in **small number of children** found buccal midazolam to be as effective as rectal diazepam in aborting convulsive SE (79% controlled with buccal midazolam vs. 59% with rectal diazepam).
- Another study of 177 children presenting to the emergency department with ongoing seizures found buccal midazolam to be more effective than rectal diazepam (56% vs. 27%) while having similar rates of adverse events.
- The efficacy of intranasal midazolam (0.2 mg/kg) is equivalent to that of IV diazepam (0.3 mg/kg) for the treatment of prolonged febrile seizures.


Step 4



Treatment Guidelines for Status Epilepticus

- Evidence-based treatment guidelines are few and far between because there are only a few randomized clinical trials.
- The **American Epilepsy Society** issued a guideline in **2016**.
- This guideline was endorsed by the Epilepsy Foundation, the Child Neurology Society, and American College of Emergency Physicians, among others.
- This evidence-based guideline proposed a treatment algorithm for management of convulsive SE in children and adults.
- It was based on an extensive literature review and rating of each article based on its class of evidence followed by translating the evidence into levels of recommendation to chiefly answer:
  - ASM efficacy as initial and subsequent therapy for SE
  - ASM adverse events
  - Comparing effectiveness between IV fosphenytoin (fPHT) and phenytoin
  - Defining refractory SE (number of ASMs after which ASM efficacy in aborting SE drops significantly).

Treatment Guidelines for Status Epilepticus

- The AES guidelines divided the seizure-time continuum into four phases of management:
  1. **Stabilization phase** (0 to 5 minutes) involves ABC management, EKG monitoring, obtaining IV access, and sending out labs including checking finger-stick glucose and reversing it as needed.
  2. **Initial therapy phase** (5 to 20) involves the use of parenteral benzodiazepines—lorazepam, diazepam, or midazolam (highest level A evidence based on three RCT mentioned above)—or in their absence the use of IV phenobarbital, rectal diazepam, or intranasal midazolam.
  3. This is followed by the **second therapy** phase (20 to 40 minutes) of second line of IV ASMs including **fPHT** (20 mg PE/kg, maximum 1500 mg PE/dose), **valproic acid** (40 mg/kg, maximum 3000 mg/dose), and **levetiracetam** (60 mg/kg, maximum 4500 mg/dose) in single doses, without any evidence to support the preference of one over the other ASM or in fact, the recommended doses in some cases (e.g., levetiracetam).
     - IV phenobarbital, if not already given during initial therapy phase, may be given as well if the above 3 second-line agents are unavailable.

Treatment Guidelines for Status Epilepticus

- The report was not able to clearly define RSE due to lack of clear evidence.
- However, it concluded that in adults, the second ASM is less effective than the first "standard" ASM in aborting SE, while the third ASM administered is substantially less effective than the first "standard" anticonvulsant (level A).
- The "substantial" less effectiveness of third ASM may be interpreted as SE reaching refractoriness after the second-line agent fails to abort the ongoing seizure.

4. This brings us to the last, **third therapy phase** (40 to 60 minutes), which also lacks evidence to guide management, but the report recommends either using another of the second-line agent or use of an IV anesthetic agent like **midazolam**, **propofol**, or **pentobarbital** under the guidance of cEEG monitoring.

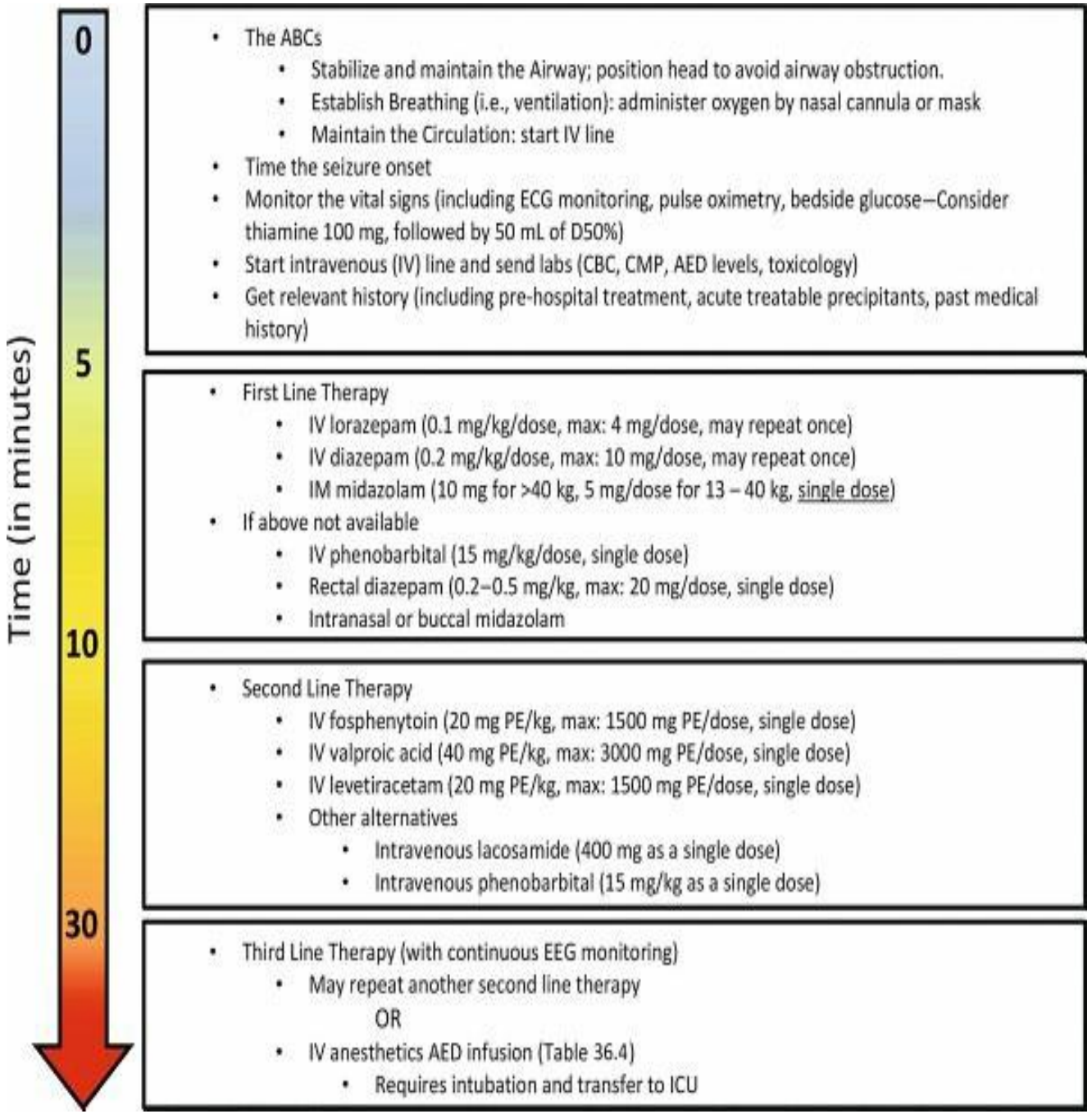
Treatment Guidelines for Status Epilepticus

- One of the highlights of the guidelines is its recommendations to use **newer-generation ASM** like levetiracetam, **which is a widely used ASM**, popular in various hospital setting due to its safety and ease of administration compared to older IV AMS agent.
- The guidelines also endorse the use of **cEEG** in the management of RSE patients.
- However, it may be argued that the suggested time line for switching of the therapy phases—initiation of benzodiazepine to the addition of second- and third-line agents—is slower than required, and a more aggressive approach toward early termination of SE is desired.

Management algorithm for SE

Evidence-based guideline

Treatmnet of convulsive SE in children and adults: report of theguideline committee of American Epilepsy Society(2016)



Primary (First-Line) ASMs for SE

- The **benzodiazepines** (lorazepam, diazepam, midazolam) are the current drugs of first choice for the initial therapy.
- Diazepam was rapidly applied to the treatment of SE soon after its discovery and has remained a mainstay of treatment.
- Theoretically, compared to lorazepam, diazepam should have a more rapid onset of action because of greater lipid solubility.
- However, this high lipid solubility results in a rapid redistribution to inactive tissues, such as fat, which can result in high rates of seizure recurrence.
- Lorazepam has been used in both adults and children.
- Although expected to have a slower time to onset than diazepam, the times of onset of lorazepam 4 mg and diazepam 10 mg in the treatment of SE in adults were similar.
- In that double-blind study, SE was controlled in 89% of episodes with lorazepam versus 76% with diazepam, with similar rates of adverse events.
- Because of a smaller volume of distribution, lorazepam should have a longer antiseizure effect and, thus, a lower rate of seizure recurrence than diazepam.

Primary (First-Line) ASMs for SE

- **In the recent prospective RCT** comparing IV lorazepam 0.1 mg/kg and IV diazepam 0.2 mg/kg, both were found to be equally effective in terminating convulsive SE in **children** (3 months to younger than 18 years) in the emergency department.
- Interestingly, at these doses, there were no differences in the rate of recurrence up to 4 hours.
- However, patients given **lorazepam** were more likely to be sedated (66.9% vs. 50%).
- Midazolam, due to its water solubility, may be administered via buccal, intranasal, or IM route if there is no IV access, and it has been associated with less sedation and respiratory depression.
- Efficacy of IM midazolam in the out-of-hospital treatment of convulsive SE in children and adults was prospectively established by the double-blind, randomized RAMPART trial.

Second-Line Agents for Status Epilepticus

- **Phenobarbital** (PB) has been used to treat SE in all age groups.
- While primarily relegated to the second line, it continues to be used as a first-line agent in the treatment of SE in the neonate.
- Respiratory depression and sedation occur.
- Caution is advised, especially when phenobarbital is administered in combination with other sedative ASMs (such as benzodiazepines).
- The loading dose for phenobarbital is 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.

Second-Line Agents for Status Epilepticus

- **Phenytoin** (PHT) may be administered by an IV loading dose in normal saline at 20 mg/kg (15 mg/kg in the elderly), which rapidly achieves a therapeutic level without respiratory depression or sedation.
- **This lack of sedation** is important for monitoring mental status(head trauma).
- The infusion rate should be 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.
- In adults, a therapeutic level should be maintained for up to 24 hours after a loading dose has been administered but may not last as long in children.
- A level obtained 2 hours after loading may help guide the timing of maintenance.
- IV PHT can cause vascular irritation, cardiac depression, and hypotension.
- If hypotension develops, the infusion rate should be decreased.
- **The purple glove syndrome**, consisting of distal limb edema, discoloration, and pain, may occur following IV phenytoin infiltration; treatment may require fasciotomies and amputation.
- It has been noted in around 1.5% to 6% of patients.

Second-Line Agents for Status Epilepticus

- For this reason, the phosphate ester **prodrug** of phenytoin, **fPHT**, is preferred.
- fPHT is dosed as phenytoin equivalents (PE) at 20 mg PE/kg.
- It can be administered in a **dextrose solution**.
- Fosphenytoin is **water soluble** and may be given by the IM route, with paresthesias and injection site pruritus as possible adverse effects.
- Bioavailability is 100%, and the conversion half-life is 7 to 15 minutes.
- Fosphenytoin is rapidly converted to phenytoin by serum and tissue alkaline phosphatases.
- A 2-hour phenytoin level is suggested to ensure conversion.
- Side effects are more likely in patients with hypoalbuminemia, renal failure, or hepatic failure and in the elderly, because of the presence of higher free phenytoin levels.
- In these patients, the infusion rate should be decreased by 25% to 50%.
- The only advantage of IV phenytoin over IV fPHT is significantly lower cost.

Second-Line Agents for Status Epilepticus

- **Sodium Valproate** (ROPAKIN®)has been available in IV form since 1995.
- Although it is not yet approved by the U.S. FDA for the treatment of SE, doses of **15 to 33** mg/kg have been administered safely in adults at a rate of 20 to 50 mg/minute.
- The AES guidelines for convulsive SE recommend doses up to **40 mg/kg.**
- It is not known to cause hypotension up to these doses.
- A systematic review of the use of IV VPA found that 70.9% of a cumulative of 860 patients had successful SE abortion.
- The probability of successful treatment with VPA was time-dependent:
  - If the VPA was given early (within 3 hours), next-line therapy with anesthesia was required in only 5%
  - But when VPA was given later, anesthesia was needed in 60%.
- A 20-mg/kg loading dose should produce a serum level of 75 mg/L.
- Overall, IV VPA is a good initial choice for second-line medication in the treatment of benzodiazepine-resistant SE and has a good side effect profile.
- However, the superiority of VPA over PHT or other second-line ASMs in controlling SE has not yet been established using a class I double-blind RCT.

Second-Line Agents for Status Epilepticus

- LEV(Aro-cetam®)is available in an IV preparation and has been used to control SE.
- Studies in healthy volunteer have shown that doses up to 2500 mg in 5 minutes and 4000 mg in 15 minutes can be given safely.
- This **favorable safety profile** is one of the reasons for its increasing popularity as a second- line agent .
- IV LEV with a mean loading dose of 944 mg (range 250 to 1500 mg) controlled **16/18** episodes of SE following benzodiazepine failure.
- A 20-mg/kg loading dose followed by 15 mg/kg BID after 6 hours controlled SE in 82% overall and in **11/12** (92%) as first-line therapy.
- Of the 50 patients, 2 (4%) developed thrombocytopenia.

Second-Line Agents for Status Epilepticus

- The **lack of a definitive answer about comparative efficacy** of the three most commonly used second-line therapies for has plagued the treatment of SE for a long time and led to nonstandardized treatment strategies and protocol.
- The recently published EcLiPSE study was the first adequately powered, multicenter, open-label randomized trial comparing the time to cessation of convulsive SE after randomization to IV **LEV** (40 mg/kg over 5 min) or IV **PHT** (20 mg/kg over at least 20 minutes) in children presenting with convulsive SE.
- Convulsive SE was terminated in **70%** of the 152 children randomized to receive LEV and in **64%** of 132 children who received PHT.
- Median time to cessation from was 35 minutes and 45 minutes, respectively.
- Overall, the frequency of adverse events was similar between the two groups.
- Although this study shows that IV LEV is a reasonable first-choice ASM for second-line treatment of pediatric convulsive SE, the use of IV PHT instead of IV fPHT makes the findings of this study less practically helpful in SE management.

Second-Line Agents for Status Epilepticus

- The highly anticipated established status epilepticus treatment trial (ESETT), published in the **late 2019** was designed to determine the most and/or the least effective treatment of benzodiazepine-resistant SE in patients >2 years of age by **comparing IV fPHT, IV VPA, and IV LEV.**
- A total of 384 patients with convulsive status epilepticus were enrolled [LEV (145 patients), fPHT (118 patients), and VPA (121 patients)].
- **The primary outcome was not statistically different between the three group**.
- In this initial report, the three drugs were associated with similar incidences of adverse events.

Second-Line Agents for Status Epilepticus

- Lacosamide (LCM) was approved by the U.S. FDA in 2008 for adjunctive therapy for focal-onset seizures.
- However, as it is available in an IV formulation, it is not surprising that it has been used for the treatment of SE with some success in both adults and children.
- A **systematic review** revealed 136 SE episodes treated with IV LCM for SE with an overall success in aborting SE achieved in 56% cases.
- A loading dose of 400 mg appears to be more effective than 200 mg in the treatment of refractory seizure clusters and SE.
- Overall emerging evidence and empirical experience suggests that LCM may be a reasonable second-line alternative in the armamentarium against SE.

Refractory SE (Management by Third-Line Agents)

- RSE occurs when seizures persist despite adequate treatment with a first- and second-line agent.
- RSE accounts for around 30% of all SE episodes.
- 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%.**
- An immediate EEG should be performed, if available; otherwise, additional empiric ASM therapy must be considered.

Refractory SE (Management by Third-Line Agents)

- After initial second-line therapy has failed, it may be reasonable to try another second-line agent prior to initiating a continuous IV infusion of an anesthetic agent.
- This is especially true in cases with nonconvulsive RSE where patient has preserved airway reflexes and stable vitals.
- IV anesthetics should be used under the guidance of **cEEG** monitoring, which is needed to help guide the infusion rate of IV anesthetics to attain the treatment goal of immediately stopping SE and prevent seizure recurrence.
- In case of unavailability of cEEG monitoring, clinical stability of the patient permitting, a transfer to facility with such capabilities should also be considered at this time point.
- It is important to recognize that continuous infusion anesthetics have been linked with several untoward effects including mechanical ventilation, hypotension, and infection as well as potentially **increasing the risk of death**.
- In contrast, a more recent study found that its use did not lead to increase in mortality but significantly increased the duration of acute hospitalization.

Refractory SE (Management by Third-Line Agents)

- The two most commonly used agents for the treatment of RSE are pentobarbital and midazolam.
- **Pentobarbital**, administered at 2 to 10 mg/kg followed by a continuous infusion, was the most widely used agent under these circumstances in the past.
- However, **midazolam**, with a shorter half-life and less sedative effects, has become a more commonly used agent in recent times.

Refractory SE (Management by Third-Line Agents)

- Another popular IV anesthetic agent used for RSE treatment is **propofol**.
- Propofol has two main advantages: a rapid onset and a short duration of action.
- It is also known to lower intracranial pressure.
- Propofol may cause metabolic acidosis and deaths have occurred secondary to **propofol infusion syndrome.**
- This syndrome is characterized by constellation of metabolic acidosis, rhabdomyolysis, renal failure, hyperkalemia, hypertriglyceridemia, and rapid cardiovascular collapse.
- Therefore, propofol should be used with caution, especially in children and ideally for a short time only (not more than 2 to 3 days), and the infusion rate should not exceed 67 µg/kg/min.
- After achievement of seizure control, another agent should be used if long-term suppression is needed.

Refractory SE (Management by Third-Line Agents)

- The **NMDA** receptor antagonist **ketamine** may also have a role in the treatment of RSE.
- Its unique mechanism of action compared to other IV anesthetics and lack of respiratory depressant effects may be advantageous in treatment of RSE/SRSE.
- Experience with its use in treatment of RSE is increasing in recent years.
- Overall, ketamine was found to be well-tolerated with many of the untoward effects that occurred during the ketamine dosing being attributed to the concurrent medications.
- A very recent systematic review of literature found 244 SE episodes, many with RSE, treated with ketamine.
- With rare adverse events, it was successful in 74% (153/207) of adults and 73% (27/37) of children.

Refractory SE (Management by Third-Line Agents)

- A critical aspect of appropriate use of above agents in RSE is that **patient should be given repeated boluses of these drugs**, under guidance of cEEG in comatose patients suspected of NCSE, until the resolution of seizure **or** the maximum dose is reached.
- **Midazolam** Load 0.2mg/kg IV(repeat q5mins until seizures stop (max load 2mg/kg)
- Other agents used include benzodiazepines like diazepam, thiopental, lidocaine, and inhalational anesthetics such as isoflurane.
- Chlormethiazole, etomidate, and clonazepam are used in Europe; paraldehyde and chloral hydrate may be administered rectally, although paraldehyde is no longer available in the United States.

Refractory SE (Management by Third-Line Agents)

- To date, no prospective study has been conducted in patients with RSE.
- Whether clinical seizures alone or both clinical and electrographic seizures need complete control is controversial.
- In this situation, many clinicians use continuous infusion anesthetics titrated to a burst suppression pattern on EEG, **aiming for complete control of both the clinical and electrographic seizures**.
- Some aim only for control of clinical seizures (without EEG monitoring).
- However, the **outcome** is not related to the extent of EEG burst suppression and is more dependent on etiology.
- Whether the goal of anesthetic use is achievement of burst suppression or background suppression, such EEG endpoint should ideally be **maintained for 24 to 48 hours** prior to initiating its slow taper.
- If SE recurs, the sequence of IV anesthetic use restarts.
- **RSE that persists or returns after 24-hour infusion of anesthetics is termed as SRSE.**

New and Rare Therapies for Status Epilepticus

- The evidence for role of newer ASMs in the management of SE is limited to reports on single-center experience.
- There is a lot of interest in the role of AMPA receptors in SE, specially due to the approval and availability of **perampanel** (PER), the first orally active noncompetitive AMPA receptor antagonist.
- A recent report on the use of PER in 30 patients with RSE, given through nasogastric tube after being crushed and dissolved in water, found that its use led to the termination of seizures in 5 (17%) patients.
- Patients had received a median of four ASMs prior to PER administration.
- The **highlight** of the study was to show that high loading dose (up to 32 mg) could be administered safely in ICU patients.

New and Rare Therapies for Status Epilepticus

- Due to its distinct 1,5-benzodiazepine structure, **clobazam** (CLB) is a benzodiazepine with some unique clinical features including lower potential for sedation.
- A recent systematic review of literature reported aborting SE in 47% of the patients.
- **Brivaracetam** (BRV) is one of the latest FDA-approved ASM.
- It is a high- affinity synaptic vesicle glycoprotein 2A–binding agent, which is structurally related to LEV.
- It is available in IV formulation of 50-mg/5-mL vial.
- Although there is not much literature on its use in SE, a recent report on seven patients discussed using a median IV BRV loading dose of 100 mg over 15 minutes.
- Two patients showed immediate clinical improvement, and two were noted to have cessation of SE on EEG.
- No cardiorespiratory adverse events were noted in this limited study.

New and Rare Therapies for Status Epilepticus

- Hypothermia, vagal nerve stimulation, and surgery have also been used for the treatment of RSE.
- **Ketogenic diet** (KD) may also have a role, especially in children diagnosed with febrile infection–related epilepsy syndrome (FIRES).
- It was recently investigated for its feasibility as treatment therapy in SRSE.
- Of the 15 adults enrolled, 14 completed the study.
- KD was given after a median trial of eight ASMs.
- Ketosis was achieved, which was the primary endpoint of this feasibility study, in all patients.
- **SRSE resolved** after a median of 5 days **after KD initiation in 11 of the 14 (79%) patients.**
- Many of the survivors were transitioned successfully to a modified Atkins diet.