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## RESEARCH ARTICLE

# STATUS EPILEPTICUS – A RECENT REVIEW

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**ABSTRACT**

Status Epilepticus (SE), a common medical emergency with significant mortality and morbidity ranging from 3-50 % in different studies. Seizures lasting for more than 5 minutes should be treated as for convulsive status epilepticus. Pathophysiological mechanisms have revealed that it is a dynamic and evolving process. Non-convulsive status epilepticus (NCSE) is status epilepticus without obvious tonic–clonic activity. Patients with NCSE have altered mental state. Refractory status epilepticus (RSE) is defined as status epilepticus that continues despite treatment with benzodiazepines and one antiepileptic drug. The goals of pharmacological therapy are to terminate seizures early and prevent recurrence. Clinical studies have shown the benefit of early administration of benzodiazepines to control status epilepticus.



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## INTRODUCTION

Status epilepticus (SE), a common medical emergency and is an important neurological condition potentially associated with significant mortality and morbidity rates. Mortality from SE varies from 3-50 % in different studies. (Ajith Cherian and Sanjeev, 2009)

### Definition

In the ILAE classification of 1981 The definition was given as: the seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur. (Proposal for revised clinical and electroencephalographic classification of epileptic seizures, 1981) From 30 min specified in the guidelines of the Epilepsy Foundation of America's Working Group on Status Epilepticus it was reduced to 20 min; the Veterans Affairs Status Epilepticus Cooperation Study stipulated 10 min and, most recently, a length of 5 min has been proposed. (Ajith Cherian and Sanjeev, 2009)

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### 1.Convulsive status Epilepticus

Lowenstein *et al*. (1998) have proposed that SE be defined as a continuous, generalized, convulsive seizure lasting > 5 min, or two or more seizures during which the patient does not return to baseline consciousness.

### 2.Non- convulsive status Epilepticus

Nonconvulsive SE (NCSE) refers to continuous or near-continuous generalized electrical seizure activity lasting for at least 30 min, but without physical convulsions. NCSE is characterized by abnormal mental status, unresponsiveness, ocular motor abnormalities, persistent electrographic seizures, and possible response to anticonvulsants. (Shorvon, 1994) Convulsive SE may evolve into the nonconvulsive form after treatment or NCSE may arise de novo.

### 3.Refractory status Epilepticus

RSE is defined as continuous or repetitive seizures lasting longer than 60 min despite treatment with a benzodiazepine (lorazepam) and another standard anticonvulsant (usually phenytoin/ fosphenytoin) in adequate loading dose. (Shorvon, 1994)

**Classification (Engel, 2006)**

| |
|---|
| I. Epilepsia partialis continua (EPC) |
| A. As occurs with Rasmussen syndrome |
| B. As occurs with focal lesions |
| C. As a component of inborn errors of metabolism |
| II. Supplementary motor area (SMA) status epilepticus |
| III. Aura continua |
| IV. Dyscognitive focal (psychomotor, complex partial) status epilepticus |
| A. Mesial temporal |
| B. Neocortical |
| V. Tonic-clonic status epilepticus |
| VI. Absence status epilepticus |
| A. Typical and atypical absence status epilepticus |
| B. Myoclonic absence status epilepticus |
| VII. Myoclonic status epilepticus |
| VIII. Tonic status epilepticus |
| IX. Subtle status epilepticus |

**Pathophysiology**

The basic processes generating status epilepticus are failure of the normal mechanisms that terminate seizures. Reduced inhibition and persistent excessive excitation causes sustain ongoing seizure activity. During prolonged seizure activity, dynamic changes in gamma-aminobutyric acid $(GABA)_A$ and N-methyl-D-aspartate (NMDA) receptor function are seen.[6] Ongoing seizure activity results in gradual reduction of $GABA_A$ receptors at the synaptic membrane following receptor internalisation into endocytotic vesicles and subsequent degradation. (Naylor *et al*., 2005) At the same time, AMPA and NMDA receptor subunits move to the synaptic membrane where they form additional excitatory receptors. This change further increases excitability in the uncontrolled seizures. (Wasterlain *et al*., 2002)

**Etiology**

The main causes of status epilepticus are low blood concentrations of antiepileptic drugs in patients with chronic epilepsy (34%), remote symptomatic causes (24%), cerebrovascular accidents (22%), anoxia or hypoxia (~10%), metabolic causes (~10%), and alcohol and drug withdrawal (~10%). (Delorenzo *et al*., 1996) In patients with SE and CNS infection, 24.3% had a refractory status that was associated with a high mortality. (Misra *et al*., 2008) Overall, about 50% of those who develop SE have no previous history of epilepsy and among the elderly about 70% have no such history.

**Clinical features**

Generalized convulsive SE is characterized by paroxysmal or continuous motor activity. The motor activity can be tonic or clonic type or a combination of both; it may be symmetric or asymmetric, and overt or subtle. However, it is always associated with impairment of consciousness and with bilateral ictal EEG discharges. (Engel, Jr. $2_{nd}$ Edition) The clinical symptoms of NCSE are protean. (Shorvon, 1994) The only symptom seen consistently is an alteration in mental state. This can range from mild confusion to profound impairment of consciousness. At times there can be fluctuation in the degree of impairment. Though psychomotor retardation is most common, agitation and excitation can also occur. Head and eye deviation, hippus, and nystagmoid eye jerks have been described. The combined sensitivity for "remote risk factors for seizures" and "eye movement abnormalities" was 100%. Focal myoclonic jerks involving the face, eyelids, or extremities have also been noted, more commonly with absence SE. Various language and cognitive difficulties like aphasia, perseverations, echolalia, confabulations have been noted. (Husain *et al*., 2003)

**Commonly used drugs that may predispose to status epilepticus by lowering the seizure threshold or by increasing the clearance of antiepileptic drugs (Ajith Cherian and Sanjeev V. Thomas, 2009)**

| |
|---|
| Antibiotics (especially in older adults or in patients with renal impairment) |
| Penicillins |
| Imipenem |
| Cephalosporins Isoniazid |
| Metronidazole |
| Erythromycin |
| Ciprofloxacin, ofloxacin |
| Antihistamines |
| Diphenhydramine |
| Antipsychotics |
| Clozapine, chlorpromazine |
| Antidepressants |
| Maprotiline |
| Bupropion |
| Tricyclics, especially clomipramine |
| Other drugs |
| Fentanyl |
| Flumazenil |
| Ketamine |
| Lidocaine |
| Lithium |
| Meperidine |
| Propoxyphene |
| Theophylline |
| Baclofen (acute withdrawal) |

**Investigation**

Although the initial diagnosis of Generalized Convulsive SE is based on clinical criteria, EEG has an important role in its diagnosis and management. Treiman and colleagues (Treiman *et al*., 1990) have described a series of five EEG patterns in status epilepticus.

| Electroencephalographic Patterns in Status Epilepticus |
|---|
| Discrete seizures with interictal slowing |
| Waxing and waning of ictal discharges |
| Continuous ictal discharges |
| Continuous ictal discharges punctuated by flat periods |
| Periodic epileptiform discharges on a flat background |

**Blood investigations in a patient with status epilepticus (Ajith Cherian and Sanjeev V. Thomas, 2009)**

| |
|---|
| Random blood sugar |
| Electrolytes - sodium, potassium, calcium, magnesium |
| Complete blood count |
| Renal function test, liver function test |
| Antiepileptic drug level |
| Arterial blood gas |

Imaging of the brain (CT scan and/or MRI) and cerebrospinal fluid (CSF) examination will be useful in patients who do not have a past history of a seizure disorder. Toxicological screen and metabolic studies for inborn errors of metabolism may be considered in children with SE when clinically indicated or when the initial evaluation reveals no obvious etiology. In non-convulsive SE an EEG is needed to confirm the diagnosis. On EEG Various pattern like repetitive generalized or focal spikes, polyspike, sharp waves, spike-and-wave or sharp-and-slow wave. (Peter W. Kaplan, 2007)

## Management

### Therapeutic principles: time is brain

SE is one situation where emergent symptomatic relief (control of seizures) takes precedence over systematic evaluation. Early initiation of intravenous anticonvulsants is crucial to successful treatment of status epilepticus.

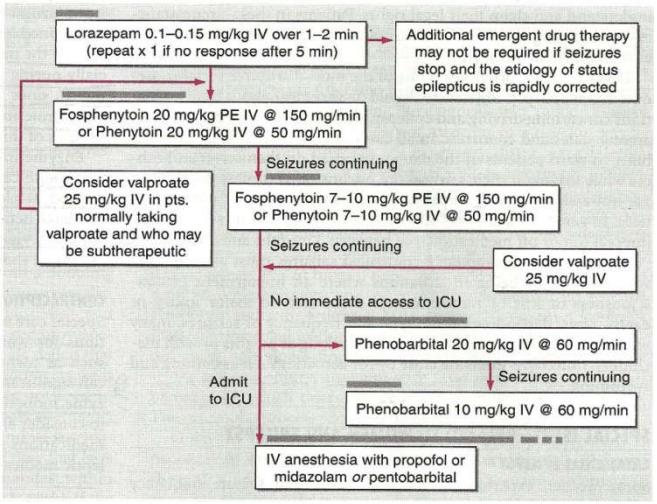
### Prehospital treatment

Rectal diazepam is safe and effective in both adults and children in the pre-hospital care of patients with frequent seizures. Serum drug concentrations peak within 3–30 min, and stay at therapeutic level for at least 8 h. (de Haan *et al*., 2010) A study of 21 adult patients with medically refractory epilepsy, 124 seizure-exacerbations were treated by their caregivers, alternatively with 10 mg Diazepam rectal solution (DZP-r) and 10 mg concentrated Midazolam nasal spray (MDZ-n), two or three treatments with each medication for each patient. No difference was demonstrated in efficacy or time to effect between the two drugs. MDZ-n was equal to DZP-r with respect to efficacy and side effects in the suppression of seizure exacerbations. The majority of patients and caregivers preferred the nasal spray over the rectal formulation. (Alldredge *et al*., 2001) Two randomized trials have been conducted in prehospital settings, comparing buccal midazolam with rectal diazepam for the treatment of continuing seizures in children and adolescents. The midazolam dose is usually 0.2-0.3 mg/kg IM/intranasal/ buccal (in children) or 10 mg in an adult. The onset of action is within 1-5 min. Buccal midazolam was found to be equally effective or better than rectal diazepam in terminating seizures, without causing any increase in adverse cardiorespiratory events or need for ventilation. Buccal or nasal preparations of midazolam are now readily available. (Ajith Cherian and Sanjeev V. Thomas, 2009) To assess the safety and efficacy of out-of-hospital administration of benzodiazepines, a randomized double-blind trial comparing intravenous (IV) diazepam (5-10 mg) or lorazepam (2-4 mg) with placebo was performed recently. The primary outcome measure was termination of SE before the patient's arrival at the emergency department. In this study, SE was terminated in 59.1% and 42.6% of patients treated with lorazepam or diazepam, respectively, compared with 21.1% of placebo treated individuals ($P$=.001). The investigators concluded that the prehospital administration of benzodiazepines was safe and effective for early termination of SE. Lorazepam appeared to be more effective than diazepam. (Marshall *et al*., 1994)

### General measures

The first step in the management of a patient with SE would be to ensure an adequate airway and to provide respiratory support with hemodynamic stability of the patient. The patient should be positioned such that self-injury is prevented during seizure activity. To avoid injuries to oral structures, one should not forcibly introduce a tongue depressor or other hard objects between locked teeth. Gentle suction can be applied to remove saliva and blood if any. Two large-gauge intravenous (IV) catheters should be inserted to facilitate fluid resuscitation and pharmacotherapy. Endotracheal intubation will be required in patients who continue to have seizures despite receiving first-line therapy. If anesthetic induction is required then Propofol or Midazolam may terminate seizure activity and facilitates intubation. Rocuronium (1 mg/Kg), a short acting non depolarizing muscle relaxant is the preferred agent. (Treiman *et al*., 1998) The drug of choice for in-hospital treatment of SE is intravenous lorazepam. Publication of the Veterans Affairs (VA) Cooperative Trial in 1998 (Alldredge *et al*., 2001) and the San Francisco Emergency Medical Services Study in 2001 (Harrison's principles of internal medicine; 18th edition) allows for an evidence-based approach to the choice of the first-line agent for use in terminating SE.

### Pharmacologic treatment of generalized tonic-clonic status epilepticus : (Shih and Bazil, 2005)




IV = intravenous ; PE = phenytoin eqivalents

### Pharmacokinetic parameters of commonly used drugs for status Epilepticus (Leppik *et al*., 1983)

| | Latency (in min) | Duration(in hours) |
|---|---|---|
| Lorazepam (IV) | 3-10 | 12-24 |
| Diazepam (IV) | 1-5 | < 1 |
| Midazolam (IM) | 5-10 | < 1 |
| Midazolam (IV) | 10-30 | 12-24 |
| Midazolam (buccal) | 5-10 | < 1 |
| Phenytoin (IV) | 10-30 | 12-24 |
| Fosphenytoin (IV) | 10-30 | 12-24 |
| Phenobarbitone (IV) | 5-30 | 48-72 |

Latency = Time interval between commencement of infusion and onset of action. Duration = The time, from onset of infusion, for which the drug may maintain adequate anticonvulsant level in the blood.

### Pharmacologic therapy

**Benzodiazepines—**Benzodiazepines are an antiepileptic medication used for the initial treatment of SE. They are a class of drugs that act at the $GABA_A$ receptor. Stimulation of this subunit leads to inhibition of neural transmission through hyperpolarization of the resting cell membrane. This is accomplished through the GABA-induced opening of chloride channels, which allows for intracellular chloride influx. Diazepam achieves higher brain concentrations and has a slightly faster onset of action, although the effect of this appears to be clinically irrelevant. (Greenblatt and Divoll, 1983) Because of high lipid solubility, diazepam is redistributed rapidly to peripheral fat stores. This property limits its clinical effectiveness to only 20 to 30 minutes and accounts for its large relapse rate. (Rey *et al*., 1999) For this reason, diazepam use for SE needs to be followed with a

second agent. Lorazepam has more favorable pharmacokinetics with a different volume of distribution and a duration of action exceeding 12 hours. Intravenous lorazepam (0.1 mg/kg) is now preferred by many investigators. Midazolam is an imidazobenzodiazepine, which gives it unique physiological properties. At pH 4, the imidazobenzodiazepine has an open ring, which makes it water soluble and thus able to be variously administered. At physiological pH, this ring closes, making it highly lipid soluble, and thus allows for rapid cerebral penetration. (Naritoku and Sinha, 2000) It has an extremely short duration of action (half life 4-6 hours) and a high recurrence rate of seizures. The various routes by which midazolam can be administered (intramuscularly, sublingually, nasally) make it an ideal agent for out-of-hospital use or when IV access cannot be obtained. Midazolam is usually started with a loading dose of 0.2 mg/kg, but increments of 0.2-0.4 mg/ kg can be given every 5 min until the seizures stop or a maximum of 2.9 mg/kg is reached. The maintenance dose is 0.1-0.2 mg/kg/h, given as an infusion to maintain electrographic suppression of seizures. One of the major disadvantages of midazolam is tachyphylaxis, because of which the dose often has to be increased several fold to maintain seizure control. Furthermore, with prolonged infusion, midazolam accumulates in the body, which may result in a prolonged time to awakening. (O'Brien *et al*., 1998)

**Phenytoin -** Phenytoin (5,5-diphenyl- 2,4-imidazolidinedione) is a barbiturate-like drug that is effective in controlling seizure activity. It limits the repetitive firing of action potentials through the slowing of the rate of recovery of voltage-activated sodium channels. Phenytoin is formulated with propylene glycol and ethanol and is adjusted to pH 12 with sodium hydroxide. It is highly protein-bound with only the free portion being metabolically active. Maintaining appropriate drug levels can be problematic because of multiple drug interactions and the saturable pharmacokinetics of hepatic metabolism and protein binding. The loading dose of phenytoin for SE is 20 mg/kg in nonglucose-containing solutions administered at a maximal rate of 50 mg/min. The most common adverse effects of phenytoin use in SE are cardiovascular, including hypotension, QT prolongation, and cardiac dysrhythmias. Most can be attenuated by reducing the infusion rate. The effects are attributable to a direct effect of both the medication and the propylene glycol used as a diluent. (Lowenstein and Alldredge, 1998) The most problematic adverse effect is severe tissue reaction that can occur with extravasation of phenytoin into adjacent tissue. The purple glove syndrome, a variant of this reaction, occurred in up to 5.9% of patients in one Mayo series. (Thomas *et al*., 1996)

**Fosphenytoin -** Fosphenytoin is a phosphate ester prodrug of phenytoin that was developed as a replacement for IV phenytoin. Fosphenytoin is water soluble, allowing easier and faster administration. It is cleared by serum and hepatic phosphatases to form phenytoin with a conversion half-life of 8 to 15 minutes. (Andrea O Rossetti and Daniel H Lowenstein, 2011) Conversion time is unaffected by serum concentrations but can be affected by low albumin states. Fosphenytoin is measured and labeled in phenytoin equivalents to avoid performing molecular-weight–based conversions between fosphenytoin and phenytoin doses. Subsequently, for every millimole of fosphenytoin administered, 1 mmol of phenytoin will be produced. Fosphenytoin can be administered at a maximal rate of 150 mg of phenytoin equivalent/min. Accounting for conversion time, peak concentrations are reached within 10 minutes of completion. Despite this rapid administration, it is unclear whether fosphenytoin controls seizures faster than phenytoin. Cardiovascular adverse effects are reduced with fosphenytoin but continue to occur. Adverse tissue effects have not been reported. Fosphenytoin is considerably more expensive than phenytoin.

**Advantages over Phenytoin:**

- pH 8 (vs Phenytoin pH 12)
- does not require solvent (Phenytoin is dissolved in propylene glycol)
- can be given IM when no IV access
- IV: - less potential for irritation – can be given faster no risk of tissue necrosis
- does not precipitate in IV solutions
- lower risk of hypotension and dysrhythmias

**Phenobarbital —**Phenobarbital is a barbiturate that prevents seizure activity by increasing $GABA_A$-mediated cellular inhibition. Its mechanism of action is similar to benzodiazepines but probably involves a different isoform of the $GABA_A$ receptor.Although phenobarbital has been shown in several series to be effective for treating SE, it is now considered a third-line drug in algorithms designed to treat SE because of its serious adverse effect profile. (Lowenstein and Alldredge, 1998) Phenobarbital profoundly depresses respiration and consciousness level with a half-life of 72 hours. In addition, it causes severe hypotension secondary to peripheral vasodilation and decreased cardiac contractility. The loading dose is 20 mg/kg IV, with a maximum infusion rate of 50- 100 mg/min.

**Valproic Acid —**Valproic acid is a short-chain fatty acid with anticonvulsant properties. Its mechanism of action is similar to phenytoin in that it appears to be mediated through a prolonged recovery of activated voltage-gated sodium channels. Other mechanisms may be mediated through valproic acid's effect on neuronal calcium channels or through its effects on GABA metabolism. The standard loading dose for intravenous administration is 25 mg/kg; but, in emergent situations, higher doses of 30- 60 mg/kg can be used. Can be administered safely in SE at a rate of 3 to 6 mg/kg/ min without adverse reactions. The chief advantage over other medications appears to be its safety profile and ease of administration. Intravenously administered valproate is found to be effective against different types of SE, including partial onset, nonconvulsive, absence, and myoclonic SE. The target serum level of valproate in SE ranges from 70 to 140 µg/ml.

**Management of refractory Status Epilepticus (RSE)**

In the VA cooperative study, (Alldredge *et al*., 2001) 55% of patients with generalized convulsive SE did not respond to first-line therapy. Probably RSE is underrecognized. This subgroup of patients has higher risk of complications and extended hospital stay and mortality. Most of them have some underlying structural cerebral damage or metabolic disorders or cerebral hypoxia. Patients with NCSE and focal motor status are more likely to enter the phase of RSE. Other risk factors include delay in receiving treatment, metabolic encephalopathy, hypoxia, and encephalitis. In the VA study, (Alldredge *et al*., 2001) the aggregate response rate to a second drug from the first-line agents was 7% and to a third drug it was only a meager 2.3%. Furthermore, the data from that study suggest that

the administration of further doses of lorazepam will not be useful. Such patients would require admission to an intensive care unit for close monitoring and more aggressive treatment under assisted ventilation.

**SE classified on basis of duration : (Hara *et al*., 1993)**

| Status Epilepticus | Duration |
|---|---|
| Impending and early SE | 5-30 min |
| Established and early refractory SE | 30 min-48 h |
| Late refractory SE | > 48 h |

**Levetriacetam**

It is new AED that had potentially important role in RSE. It is available as an intravenous preparation that can be infused rapidly. In some of the pioneering studies, seizure control has been achieved in patients with RSE by administration of levetiracetam (3000 mg/day). It is currently approved for intravenous use in a dosage of up to 3000 mg given over 15 min.

**Propofol**

Propofol is an alkylphenol (2,6-diisopropylphenol) that has been used extensively for the induction and maintenance of anesthesia and for sedation in the intensive care unit. Propofol is a global CNS depressant. It directly activates the GABA receptor. (Stecker *et al*., 1998) In addition, propofol inhibits the NMDA receptor, modulates calcium influx through slow calcium ion channels, and has antioxidant activity. The excellent pharmacokinetics and favorable adverse effect profile makes propofol the ideal drug to treat RSE. The two main advantages of propofol are a rapid onset and short duration of action. Propofol is a highly lipophilic agent with a large volume of distribution. This property results in its rapid uptake and elimination from the CNS, thereby giving it rapid onset of action and allowing rapid recovery upon discontinuation. Recovery is rapid even after prolonged use. No dose reduction is required in patients with hepatic or renal disease. Benzodiazepines, when administered concomitantly with IV propofol, have a dose-sparing effect on propofol and so lower doses can be equally effective. The usual loading dose ranges from 3-5 mg/kg but loading doses as high as 10 mg/kg have been safely used. This should be followed by a maintenance infusion at the rate of 30-100 μg/kg/min, which should be titrated to burst-suppression pattern. SE stops within 10 min in most situations. After 12 h of seizure suppression, the dose can be gradually reduced by 50% over the next 12 h and if there is no relapse it can be withdrawn slowly over the subsequent 12 h. If seizures relapse during the weaning period, a further loading dose of 1-3 mg/kg can be administered and the maintenance infusion can be continued until a 12-h seizure-free period occurs. (Kang, 2002) The most severe complication associated with propofol is the "propofol infusion syndrome". It is a rare complication that occurs when the dosage exceeds 5 mg/ kg/h for more than 48 h. The propofol infusion syndrome is a potentially fatal condition characterized by severe metabolic acidosis, hyperlipidemia, rhabdomyolysis, and cardiovascular collapse. It is currently recommended that the dosage of IV propofol should not exceed 100 μg/kg/min in adults. Other contraindications include allergy to soybean oil, egg lecithin, or glycerol. It should be used with caution in combination with carbonic anhydrase inhibitors such as zonisamide and topiramate due to the risk of refractory acidosis.

**Thiopental**

The anaesthetic barbiturate thiopental, or its metabolite pentobarbital, are the oldest compounds used in this setting. In addition to GABAA modulation, barbiturates have an NMDA-antagonist action in vitro, which might be of use in view of the pathophysiological mechanisms of RSE. (Zhan *et al*., 2001) They have a long half-life (up to 36 h) after continuous administration, owing to a tendency to accumulate in adipose tissue. This accumulation can become challenging, especially in older patients with pre-existing cardiovascular problems.

**Inhalational anesthetics**

Inhalational anesthetics offer an alternative approach to the treatment of RSE. Isoflurane and desflurane are the two agents that have been tried in the treatment of RSE because of the safety associated with their long-term administration. Isoflurane is the agent of choice for RSE. Isoflurane undergoes significantly less metabolism in the liver than halothane. Both inhalational agents can cause dose-dependent reduction in blood pressure due to peripheral vasodilation and an inotrope and/or vasopressor may be required during their administration, besides adequate fluid resuscitation.

**Prognosis**

SE has a variable prognosis. In large hospital-based studies, mortality varies from 3-50%. The factors associated with high mortality include refractory seizures, acute symptomatic etiologies (e.g., hypoxia or central nervous system infections), impairment of consciousness, longer duration of SE, and older age (> 70 years). Cardiovascular decompensation during SE, medical complications, and overtreatment with AEDs may also predispose to excess mortality. Coma with recurrent electrographic status and multiorgan dysfunction carries poor clinical outcome. Seizure duration was the single major predictor of mortality on multivariate analysis in one study, with a duration < 10 h resulting in lower mortality (10%) and a duration > 20 h in high mortality (85%). Outcome in RSE is poor; mortality is almost 50%, and only a minority of patients (primarily those with preexisting epilepsy and no acute brain process) return to their premorbid functional baseline.

**Conclusion:** SE is a medical emergency that need to be evaluated and managed in a systematic manner. There is a strong consensus about the need for an early, effective treatment to prevent morbidity and mortality. Patients who have persistent generalized seizures beyond 5 min deserve to be treated as SE. It is important to initiate treatment as soon as the patient is observed, preferably in the prehospital phase itself in order to prevent resistance to medications. Those patients who have failed to respond to two of the first-line drugs (lorazepam and phenytoin in most instances) need to be managed as Refractrory SE. Such patients should be moved to intensive care unit, where they could be administered second-line drugs (barbiturates or benzodiazepines), with ventilator support and continuous EEG monitoring. If there is no facility for intubation, they can be treated with non sedating medications such as intravenous valproate, levetiracetum. Non convulsive SE should be kept in mind in patients with prolong coma and should be adequately treated. It is equally important to attend to the general medical condition of the patient, even as the AEDs are being administered.

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