**Status Epilepticus**

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### Abstract

Status epilepticus (SE) is a neurological emergency resulting from prolonged clinical or electroencephalographic seizure activity. Refractory SE refers to the persistence of seizure activity despite the initiation of first- and second-line anticonvulsant therapy. Sinister outcomes are often attributed to the etiology of SE. Despite randomized multicentre trials of established and promising therapeutic options, the management and prognostication in SE are fraught with challenges. Neither the duration of SE nor time-delay to initiation of therapy should discourage the aggressive approach to the management of SE. Neurointensive care of patients with SE consists of an algorithmic approach tailored to the etiology and systemic complications that arise as a consequence. This approach is also driven by the persistence of electrographic seizure activity, which is best followed with continuous EEG monitoring. The extent of patient support has to be augmentative to the degree of encephalopathy/coma and impairment of vital functions. Potential interactions of anticonvulsant drugs with other co-medications need to be considered during the course of treatment. This review discusses the existing literature on the epidemiological aspects, clinical approach, treatment and prognostication of SE.

### Introduction

Status epilepticus (SE) in simple terms is used to describe a series of uninterrupted seizures which result in an impairment of normal brain function, which if not treated as a medical emergency results in high morbidity and mortality.1-3 SE is one of the most common medical emergencies, with an overall annual incidence of 10-41 per 100,000.1-4 The incidence of SE has shown a decreasing trend in both developing and developed countries over the years. Age-specific incidence rates of SE show a U-shaped curve with a bimodal distribution peaking in very young and the elderly.7

### Definition and Classification

The International League against Epilepsy (ILAE) has defined SE as “a seizure that persists for a sufficient length of time, or repeated frequently enough that recovery between attacks does not occur”5, 6. However, the definitions and classifications are still evolving and an ILAE task force is currently developing a new draft on a definition and classification of SE.5 For the purpose of this review, we classify SE based on the presence or absence of motor manifestation into convulsive and non-convulsive (Figure 1).10 A third category is often recognized comprising the boundary syndromes including epileptic encephalopathies and acute forms of coma with status-like electroencephalography (EEG) patterns.

### Convulsive SE

Convulsive SE generally refers to the generalized tonic-clonic SE which is the most dangerous type of SE. Generalized convulsive SE classically has been defined as recurrent generalized convulsions without full and complete recovery of consciousness between seizures or as a single prolonged convulsion without the characteristic evolution of a single discrete seizure.11 The definition of duration of convulsive SE has been a subject of controversy over the years. Most authors have suggested a seizure activity lasting 30 minutes for defining SE. However, for practical purposes, a duration of 5 minutes as proposed by Lowenstein et al.11 may be better adopted for adults and children aged above 5 years.

### Non-convulsive SE

Non-convulsive SE is a state of electromechanical dissociation where the epileptiform discharges evident on the EEG are not accompanied by clinical manifestations other than obtundation, hardly discernible motor manifestations or coma.12 Non-convulsive SE has long been subdivided into 2 categories: absence status and complex partial status. Patients with non-convulsive SE need to be managed as convulsive SE, using EEG as a guide rather than clinical observations as the determinant of response to treatment.

### Phases of SE

The physiological changes in SE evolve in two phases: the first is the compensated stage during which cerebral damage is prevented by the physiologic mechanisms which compensate the increased metabolic demands because of seizures. After 30 to 60 minutes of continuous seizures, the patient moves into the second or the decompensated stage when these compensatory mechanisms are overwhelmed and there is potential for neuronal injury with persistence of seizures.13 The cerebral damage is caused by systemic and metabolic disturbances (hypoxia, hypoglycemia, acidosis and raised intracranial pressure) and also by the direct excitotoxic effect of seizure discharges, which result in calcium influx into neurons and a cascade of events resulting in necrosis and
management strategies.15 SE evolving in three sequential stages is useful in deciding the treatment till the status becomes established. The concept of ongoing neuronal injury in SE, it is prudent not to delay the timing of therapeutic interventions in SE.

Duration

The duration of seizures which qualifies for SE has long been a subject of debate. New evidences are now coming up based on animal research as well as anecdotal evidence from humans. Data from animal studies indicated that repetitive seizures become self-sustaining and pharmacoresistant and can produce neuronal injury within a period of 15 to 30 minutes.14

Stages

As there is time-dependent development of pharmacoresistance and ongoing neuronal injury in SE, it is prudent not to delay the treatment till the status becomes established. The concept of SE evolving in three sequential stages is useful in deciding the management strategies.15

Impending SE: This is defined as continuous or intermittent seizures lasting more than 5 minutes without full recovery of consciousness between the seizures. In the study by Theodore et al.,16 it was noted that the duration of a single seizure never exceeded 2 minutes and a cut-off of 5 minutes is 18 standard deviations from the mean duration. In the Richmond study, 40% of seizures lasting between 10 to 29 minutes were shown to stop spontaneously without treatment, thereby indicating that all seizures exceeding the 5 minute mark may not proceed to established SE, but still pose a high risk for it.17

Established SE: This is defined as clinical or electrographic seizures lasting more than 30 minutes without full recovery of consciousness between the episodes. Animal data has proven that by 30 minutes, the seizures become self-sustaining; produce distinct seizure-induced neuronal damage and become more pharmacoresistant.18

Subtle SE: When a generalized convulsive SE is prolonged or after treatment in an active manner, both the motor as well as electrographic activity becomes subtle although there is likely to be continuing neuronal damage warranting an active ongoing treatment.19

Pathophysiology

In experimental settings, recurrent seizures exhibit the tendency to become self-sustaining even after the removal of the epileptogenic stimulus in the mature brain. The available data leads us to assume that similar mechanisms operate in human brain. The initial phases of SE can be easily terminated by drugs which augment inhibition or depress excitation of the membrane potential.18,19 But once the SE becomes established, only certain drugs remain effective especially those inhibiting the glutamatergic transmission.20 Those acting via potentiating GABAergic transmission have 20 times reduction in potency after 30 minutes of seizure activity.21 Basic pathophysiologic mechanisms which operate during SE are due to changes at the molecular level mainly involving protein phosphorylation. The initial changes occur at the level of the neurotransmitter receptors and neuronal plasticity which alter the protein expression. There is also a receptor trafficking taking place in the form of externalization or internalization of the receptors. During SE, there is decrease in the GABA receptor subunits and increase in the NMDA glutamate receptor subunits on the membrane surface.22 In addition, recent data have implicated other mechanisms operating at the receptor level like acute down-regulation of adenosine A1Activity, which contributes to overexcitation.23 Changes in gene expression come to play later and are partly annulled by the inhibition of protein synthesis. Maladaptive changes occur in protein expression which may contribute to the self-sustaining nature of the events. There is depletion in hippocampus of the predominantly inhibitory peptides dynorphin, galanin, somatostatin, and neuropeptide Y whereas the expression of the proconvulsant tachykinins, substance P and neurokinin B is increased. Seizure-induced neuronal death continues to occur even when motor manifestations are absent due to excitotoxic mechanisms which produce cell death.22,23

Etiology

According to etiology, SE can be classified into: 1) Acute symptomatic: SE related to an acute medical or neurological illness; 2) Remote symptomatic: SE owing to conditions resulting in a static encephalopathy or an antecedent insult such as stroke; 3) Cryptogenic: SE presumed to be symptomatic, but the cause is unclear; and 4) On the background of an established epilepsy.

The etiologies causing SE is distinctly different in developing and developed countries, although in both scenarios acute symptomatic etiology ranks as the major cause of SE. Cerebrovascular disease is the predominant etiology in developed countries, whereas in developing countries CNS infections account for the majority, varying between 20-67% in various studies.24-31 A systematic review by Neligan and Shorovon showed that the most common underlying causes were cerebrovascular disease and low antiepileptic drugs (AED) levels. A relatively good outcome was noted when the etiology is low AED levels, metabolic conditions and alcohol-related SE, whereas a worse prognosis was seen when the etiology was acute symptomatic with cerebrovascular disease or CNS infections especially in the setting of cerebral anoxia.8 The common etiologies are enlisted in Figure 2.

In a prospective study from India by Murthy et al31 the etiology was acute symptomatic in 54%, remote symptomatic in 7%, and cryptogenic in 19%. In 20% of patients, it was due to antiepileptic medication non-compliance. Of the acute symptomatic SE, central nervous system infections (neurocysticercosis, encephalitis or meningoencephalitis) were the risk factor in 52% patients.31
Treatment

The principles of management of recurrent seizures are to identify and correct reversible causes, maintenance of cerebral and systemic homeostasis and prompt termination of SE.

Prehospital Management

The studies which have looked into the prehospital management of SE have shown that rectal diazepam (15-20 mg as rectal gel) to be useful and safe in both adults and children. Other drugs which have been tried are intravenous lorazepam (2 mg) and diazepam (5 mg) which have a relatively good safety profile. Although these drugs are preferred intravenously if possible, intramuscular route is also found to be effective in the prehospital setting. However, these should be administered only by trained paramedical personnel. The other alternatives which are being used recently are buccal or nasal midazolam.

Table 1: Antiepileptic drugs used in the treatment of status epilepticus and their doses

<table>
<thead>
<tr>
<th>Antiepileptic drug</th>
<th>Dose</th>
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<tbody>
<tr>
<td><strong>First Line (IV)</strong></td>
<td></td>
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<tr>
<td>Lorazepam</td>
<td>0.1mg/kg bolus @ 2mg/min</td>
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<tr>
<td>Diazepam</td>
<td>0.2mg/kg bolus @ 4mg/min</td>
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<tr>
<td>Midazolam</td>
<td>0.05-0.2mg/kg @ 2mg/min</td>
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<tr>
<td><strong>Second Line (IV)</strong></td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td>15-20mg/kg @ 50mg/min; Maintenance= 4-7mg/kg/day (IV/PO)</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>15-20mg/kg PE @ 75-150mg/min</td>
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<tr>
<td><strong>Third Line (IV)</strong></td>
<td></td>
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<tr>
<td>Levetiracetam</td>
<td>20-30 mg/kg bolus over 15 minutes, followed by maintenance dosing 1500 mg BID (IV/PO)</td>
</tr>
<tr>
<td>Sodium Valproate</td>
<td>15-30 mg/kg bolus @ up to 6 mg/kg/min, followed by maintenance dosing 500 mg TID (IV/PO)</td>
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<tr>
<td>Phenobarbital (ventilator on stand-by)</td>
<td>20 mg/kg bolus @ 75 mg/min, followed by initial maintenance dosing 60 mg TID (IV/PO)</td>
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<tr>
<td>Phenobarbital Level= 20-40 μg/ml</td>
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</tr>
<tr>
<td>Lacosamide</td>
<td>200mg @ 50mg/min; 200mg BID (IV/PO)</td>
</tr>
<tr>
<td><strong>Fourth Line (cIV)</strong></td>
<td></td>
</tr>
<tr>
<td>Midazolam (optional third line treatment if ventilator on stand-by)</td>
<td>Loading: 0.1-0.2 mg/kg (max, 10 mg at a time) Repeat bolus - If clinical seizures persist 5 min after initial bolus, then administer additional bolus of 0.2 mg/kg bolus &amp; continue infusion. Repeat bolus every 5 min till total midazolam bolus dose reaches 2 mg/Kg</td>
</tr>
<tr>
<td>Maintenance cIV dose: 0.05-0.4 mg/kg/h</td>
<td></td>
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<tr>
<td>Maximum cIV dose: increase infusion rate (with each bolus) of midazolam by 0.05 to 0.1 mg/kg/hr to a maximum infusion rate of up to 3 mg/kg/hr.</td>
<td></td>
</tr>
<tr>
<td>Thiopental sodium</td>
<td>Loading: 3 to 5 mg/kg at 0.2-0.4 mg/kg/min</td>
</tr>
<tr>
<td>Maintenance cIV dose: 3.0 -5.0 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>Maximum cIV dose: 5.0 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>Loading: 1-2 mg/kg at 10 mg/min</td>
</tr>
<tr>
<td>Maintenance cIV dose: 2-10 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>Maximum cIV dose: 15 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>Topiramate (PO)</td>
<td>10 mg/kg NG loading dose followed by 5 mg/kg NG divided b.i.d. Dose range: 300 mg -1,600 mg.</td>
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</table>

Note: IV= Intravenous route of administration; cIV= Continuous intravenous infusion; BID= twice daily; TID= thrice daily; PE – Phenytoin equivalent dose (1.5 times of phenytoin dose); PO= Peroral route; NG- Nasogastric route of administration
General Emergency Measures

The maintenance of airway, breathing and circulation is the priority in patients presenting with SE. The reversible factors which should be kept in mind that include hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia, acidosis, hyperthermia and hypoxia. If alcoholism is suspected, patient should be given a bolus dose of 100 mg thiamine followed by dextrose infusion. Hypoxia may not be clinically manifest and oxygen supplementation is recommended in all patients in SE. Emergency investigations should include the following: blood gases, glucose, renal and hepatic functions, calcium, magnesium, full blood count, clotting screen, and AED concentrations. Serum should be stored for toxicology or virology or other future analyses. An electrocardiogram should be performed.

Antiepileptic Drug Therapy in SE

All treatment protocols in SE are based on a staged approach (33,34). The AEDs used in SE can be broadly divided into first and second line drugs. The detailed protocol of therapy and the dosages are provided in Figure 3 and Table 1.

First-line drugs

Randomized controlled trials comparing the efficacy of first-line medications in SE are scarce and hence the protocols for management are heterogeneous. In early SE, the drug of choice is intravenous benzodiazepines.33 Administration of intravenous benzodiazepines, lorazepam or diazepam has shown similar benefits in studies although the safety profile may be slightly in favor of the former. Intravenous midazolam is also being increasingly used, but has not been studied in any double-blind randomized trial.33 Pertinent to the first-line management would be the issue of respiratory or hemodynamic compromise that may be incurred during bolus dosing with benzodiazepines or phenytoin, especially in children and the elderly. Recent studies including an open labelled randomized study from India have emphasized equivalence of efficacy and safety of levetiracetam in comparison to first line AED like lorazepam.36,37 Though cost of therapy is an issue, availability as an intravenous preparation, favourable pharmacokinetic profile and longer duration of action of levetiracetam could make it an acceptable alternative as a first line agent during a cluster of seizures or SE in a hemodynamically unstable patient.

Second-line drugs

Once the SE is established, intravenous AEDs need to be administered. The agents available are phenytoin, valproate and levetiracetam.33 Intravenous fosphenytoin or phenytoin is generally preferred world-over as first choice if the seizures are not controlled with benzodiazepines. Fosphenytoin is preferred over phenytoin due to the favorable side effect profile especially lack of thrombophlebitis. In a comparative trial of phenytoin, valproate and levetiracetam, phenytoin was not statistically different in efficacy from the other two and levetiracetam was found to be less efficient than valproate to control SE.

The other parenteral AEDs available recently is lacosamide, but data on its effectiveness and its comparative efficacy with other drugs are not available presently.39,40 There are no head to head comparative prospective trials between them. A few randomized studies from India with either one or two of them displayed almost similar efficacy especially between phenytoin and valproic acid,41,42 although there are no studies comparing levetiracetam or lacosamide with these agents from India. Topiramate orally was compared with phenytoin in one randomized trial and was found to be equally effective in adults.43 Therefore, in the absence of clear rational evidence so far, an experienced physician can choose pragmatically from one among them as the clinical situation warrants. They have to be continued in the oral form once the seizures are controlled.

Refractory SE

There is no single well-accepted definition for refractory SE. For practical purposes, when adequate doses of two intravenous anticonvulsants fail to terminate seizures, the status is said to be refractory. At this stage general anesthetic medications are used for the control of seizures after intubating the patient.34 With the use of these agents, majority of SE will get controlled, and hence the failure of therapy is usually attributable to dose-limiting side effects or due to an inadequate target dose. Withdrawal seizures while tapering the drugs are reported in 0.3% to 9% cases.33

The various drugs used in refractory SE are midazolam, thiopental sodium/pentobarbital and propofol,35,44 Of these, there is a trend towards more preference for midazolam in that the control of seizures, lesser rate of withdrawal seizures and fewer side effects are exhibited by this drug as compared to the other two.44 Propofol is associated with potentially fatal ‘propofol infusion syndrome’ produced by depression of cellular and mitochondrial functions and is commonly seen in children and patients co-medicated with catecholamines and steroids. Thiopentone anesthesia was more commonly associated with death, which may be a reflection of the severity of the status. The end point of anesthetic treatment in SE is to achieve burst-suppression pattern in the EEG.

Super-refractory SE

Super-refractory SE is a relatively newer terminology used to define SE that continues for 24 hours or more after the initiation of anesthesia, including those cases in which the SE recurs on the reduction or withdrawal of anesthesia.45 Ketamine infusion was studied in a small group of patients with super-refractory SE and 82% achieved satisfactory control. Inhalational anesthetics, isoflurane and desflurane were also found to be useful for initial control in small case series.45

Intravenous magnesium has excellent efficacy in the treatment of seizures due to eclampsia and in congenital or acquired hypomagnesemia. Serum magnesium level should be done in all patients with refractory SE. Pyridoxine is effective in SE related to pyridoxine deficiency. Immunosuppressive regimens like steroids, intravenous immunoglobulin, and plasma exchange may be effective as many of the refractory seizures have occult immunologic causes. Ketogenic diet has effect in SE related to epileptic encephalopathies. Hypothermia of 32 to 35°C, preferably delivered by endovascular cooling is an effective measure and affords neuroprotection as well, but one should be aware of the various systemic complications.45

Neurosurgery has been used in many centers for refractory SE and is mainly targeted against the etiology of the seizures. Resection of cortical dysplasia is the most frequently performed surgery. Magnetic and electrical stimulation therapies like transcranial magnetic stimulation, vagus nerve stimulation, deep brain stimulation and electroconvulsive therapy are experimental forms of treatment used in SE.45

Outcome

Mortality from SE in various studies is up to 20%,1,5,33 Major determinant of the outcome in SE is the underlying etiology and
is not related to the type of medications used or duration of SE. In one study which specifically looked into the duration elapsed before instituting correct treatment in SE, a duration of less than 10 hours was associated with a better overall outcome, but this was not significant once etiology, presentation in a comatose state and type of SE were accounted for. In a study on convulsive SE from India by Murthy et al., the overall mortality was 10.5%, with lack of response to first-line treatment being a predictor of mortality (p < 0.001). Also, longer duration of seizures was associated with increased morbidity (p=0.001). These facts reflect on the importance of emergent treatment of SE by medical/para-medical staff at the primary health care contact point.

Study of SE in 84 patients from our Institute over a period of 10 years showed the distribution of types of SE as convulsive SE in 90.7%, non-convulsive SE in 6.5%, and myoclonic SE in 2.8%. Majority (60%) events were remote symptomatic. Mean delay between onset of SE and initiation of treatment was 12.8 hours and only in 11% events, appropriate treatment was started within 1 hour of onset of SE. In 79% of events, SE could be aborted with use of first- and second-line drugs. Case fatality rate was 11%, 22% developed neurological sequelae and 67% returned to baseline. Acute symptomatic SE, older age, sensorium at the time of admission and delayed hospitalization were predictors of poor outcome.

Conclusions
For the general physician, recognition of SE in both its convulsive and non-convulsive or subtle forms is of paramount importance. Prompt initiation of first- and second-line therapy is critical for management of this devastating condition and early referral is important when ventilatory care and intravenous anesthesia are anticipated. The role of emergent EEG cannot be overemphasized not only in the recognition of non-convulsive SE but also when continuous intravenous therapy is to be initiated with midazolam or barbiturates. Diagnosis and management of the precipitating event are likely to determine the outcome of SE related to acute symptomatic etiologies. Primary health care centers should be equipped with basic facilities for the initial management of SE. With more and more governmental and nongovernmental ambulance service facilities becoming available in major cities and towns, pre-hospital treatment of SE needs emphasis. These measures, hopefully, will improve the outcome of SE in terms of both the morbidity and mortality during the coming years.

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