Chapter 117
Convulsive Status Epilepticus: Treatment

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INTRODUCTION
Status epilepticus (SE) refers to a condition in which there is a failure of the "normal" factors that serve to terminate typical seizures, and is a common neurological emergency associated with high mortality and morbidity. It may be classified based solely on the presence or absence of convulsions, into convulsive SE (CSE) and nonconvulsive SE (NCSE). It requires emergent, targeted treatment to reduce the associated morbidity and mortality. The underlying etiology is the important determinant of mortality in SE. This review will discuss the evaluation and management of CSE.

DEFINITION
Traditionally, CSE has been defined as "continuous seizure activity lasting 30 minutes or as two or more discrete seizures between which consciousness is not fully regained." The new proposed operational definition for adults and older children (> 5-year-old) is "a continuous, generalized, convulsive seizure lasting more than 5 minutes, or two or more seizures during which the patient does not return to baseline consciousness." This new definition is based on the observations that spontaneous cessation of generalized convulsive seizures is unlikely after 5 minutes.

The exact definition of refractory SE (RSE) is unclear and the commonly used definition is "seizure activity that continues after first- and second-line therapies have failed." Most experts agree that patients should be considered in RSE after failure of adequately dosed initial benzodiazepine and one antiepileptic drug (AED). Duration of SE after initiation of treatment is no longer considered as a criterion for classification of RSE.

INCIDENCE
In a systematic review, the reported incidence rates of CSE vary between 3.86 and 38 per 100,000 per year in children and 6–27 per 100,000 per year in adults. The incidence has a bimodal distribution with peaks in children aged less than a year, with 135–156 per 100,000 and in the elderly, 14.6–86 per 100,000. Estimates of the frequency of RSE in patients with SE have ranged from 31 to 44%. There are no community based incidence studies in CSE from India.

ETIOLOGY
In adults, SE is more often of acute symptomatic etiology and the common etiologies include: central nervous system (CNS) infections, acute strokes, hypoxic encephalopathy, metabolic causes and low AED levels. No clear etiology can be identified in 20% of cases. Of the acute symptomatic etiology, cerebrovascular disease is the predominant cause in developed countries, more so in the elderly.

In India and other developing countries, CNS infections account for 28–67% of the etiological spectrum. Determining the underlying etiology is very essential as it is an independent predictor of both mortality and morbidity.

Mortality and Morbidity
The reported mortality at hospital discharge in CSE is 9–21%, at 30 days: 19–27%, and at 90 days: 19%. The short-term mortality (all age groups) rates reported from India and other developing countries range between 10.5% and 28%. Convulsive status epilepticus results in severe neurological or cognitive sequelae in 11–16% of patients. Factors associated with poor outcome after generalized CSE include: underlying etiology, de novo development of SE in hospitalized patients, older age, impairment of consciousness, duration of seizures, focal neurological signs at onset and the presence of medical complications.

TREATMENT
Repeated seizures cause an internalization of gamma-aminobutyric acid (GABA) receptors, together with a movement of N-methyl-D-aspartate (NMDA) receptors to the synapse. This explains the time-dependent development of pharmacoresistance to GABAergic drugs. Gamma-aminobutyric acid (GABA) agonists with NMDA antagonists and with agents acting at other sites are successful in treating experimental SE, and in reducing SE-induced brain damage and epileptogenesis. This basic knowledge suggests that the rational drug treatment in SE should aim at multiple receptors or ion channels to increase inhibition and simultaneously reduce excitation.

For the patients with CSE, it is helpful to plan therapy (Flow chart 1) in a series of progressive stages. While selecting AEDs, the pharmacokinetics for use in SE is to be considered. These include ease of administration, onset of action (rapid), duration of action (intermediate to long), spectrum of activity (broad) and minimal morbidity.

- **Premonitory stage**: Prolonged epileptic seizure (out-of-hospital) (5 minutes)
- **First stage**: Out-of or in-hospital (5–20 minutes)
- **Second stage**: Established SE (20–60 minutes)
- **Third stage**: Refractory status epilepticus (> 60 minutes).

Treatment of CSE should occur rapidly and continue sequentially until clinical and electrographic seizures are halted. Critical care treatment and monitoring (Table 1) should be started simultaneously with emergent initial therapy and continued until further therapy is considered successful or futile.
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Continuous Electroencephalography Monitoring in Status Epilepticus

Treatment of SE in the intensive care units (ICUs) usually requires continuous electroencephalography (cEEG) monitoring to direct treatment. It should be initiated within 1 hour of SE onset, if ongoing seizures are suspected. It is suggested to use maintenance AEDs and monitor for recurrent seizures by cEEG monitoring during titration period. If the patient is being treated for RSE at a facility without cEEG capabilities, consider for transfer to a facility with cEEG monitoring. The indications for cEEG monitoring in SE are: recent clinical seizure or SE without return to baseline more than 10 minutes; coma, including postcardiac arrest; epileptiform activity or periodic discharges on initial 30 minutes EEG; and suspected nonconvulsive seizures in patients with altered mental status. Duration of cEEG monitoring should be at least 48 hours in comatose patients to evaluate for nonconvulsive seizures. The treatment endpoints for cEEG monitoring are: cessation of nonconvulsive seizures; diffuse beta activity; burst suppression 8–20 seconds' intervals; and complete suppression of electroencephalography (EEG).

**Flow chart 1:** Convulsive status epilepticus (CSE): Treatment algorithm

- Recurrent seizures lasting more than 5 minutes
  - Alternative drug
    - Valproate 40–60 mg/kg at a rate of 6 mg/kg/minute
  - cEEG monitoring should be done at this stage

- Lorazepam 0.1 mg/kg IV (maximum 4 mg); repeat lorazepam after 5 minutes if seizures do not terminate
  - Alternative drug
    - Phenobarbital 15–18 mg/kg (50 mg/minute) or fosphenytoin 15–18 mg/kg phenytoin equivalent (PE) (150 mg/minute)
  - Repeat phenytoin 5–10 mg/kg or fosphenytoin 5 mg PE/kg IV if seizure persists after 10 minutes
    - Midazolam 0.2 mg/kg IV load followed by 0.1–2.0 mg/kg/hour or propofol 1–2 mg/kg IV load followed by 2–10 mg/kg/hour infusion
    - If seizures persist even after 24 hours, try the emerging novel therapies
      - Ketamine bolus: 0.5–4.5 mg/kg infusion: up to 5 mg/kg/hour; Immunomodulation IV methyl prednisolone or IV Ig; resective surgery; ketogenic diet; hypothermia

- Levetiracetam 20–30 mg/kg at 5 mg/kg/minute (maximum 3,000 mg)
  - Hemodynamic monitoring: Monitor for complications and treat

**Abbreviations:** IV, Intravenous; cEEG monitoring, Continuous electroencephalogram monitoring; Ig, Immunoglobulin

**TABLE 1 | Status epilepticus: Monitoring and critical issues**

**First stage (5–20 minutes):**
- Oxygen supplement; obtain IV access, stabilize airway, respiration and hemodynamics as needed; monitor ECG and SpO₂
- Thiamine 100 mg IV; 50 mL of 50% dextrose unless adequate glucose known. In children less than 2 years pyridoxine
- Investigations: Random blood glucose, LFT, RFT, electrolytes and BUN, toxicology screening, magnesium, phosphorous, CSF if CNS infection a diagnostic possibility, and CT/MRI

**Second stage or established GCSE (20–60 minutes):**
- Cardiorespiratory function monitoring: ECG, blood pressure, SpO₂; Pressors if needed, identify and treat medical complications, treat acidosis
- Investigations: cEEG monitoring, if the facilities are available

**Refractory status epilepticus (> 60 minutes):**
- Shift to ICU with facility for hemodynamic monitoring and cEEG monitoring, identification and treatment of medical complications including hyperthermia
- Consider treating acidosis if pH is 7.2 or if symptomatic

Abbreviations: IV, Intravenous; ECG, Electrocardiogram; SpO₂, Pulse oximeter oxygen saturation; LFT, Liver function tests; RFT, Renal function tests; BUN, Blood urea nitrogen; CSF, Cerebrospinal fluid; CNS, Central nervous system; CT, Computed tomography; MRI, Magnetic resonance imaging; GCSE, Generalized convulsive status epilepticus; EEG, Electroencephalogram; cEEG, Continuous electroencephalography; ICU, Intensive care unit

**Continuous Electroencephalography Monitoring in Status Epilepticus**

Benzodiazepines are the drug of choice for out-of-hospital treatment. Lorazepam is the drug of choice for intravenous (IV) administration, and midazolam for intramuscular (IM) administration.26–31 Rectal diazepam has been shown to be effective in children.26 Other options, both in children and adults include buccal midazolam27 and intranasal midazolam.29–31 prehospital treatment of SE (PHTSE) trial showed a clear benefit of active treatment with either diazepam or lorazepam over placebo, with a trend favoring lorazepam over diazepam.28

**First Stage/Out-of or In-hospital (5–20 Minutes)**

The veteran affairs (VA) cooperative study demonstrated advantage of IV treatment with lorazepam over phenytoin. However, there were
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Lacosamide is a novel anticonvulsant drug that acts by slow inactivation of the voltage-gated sodium channel, and is available as infusion. Case reports suggest that lacosamide may have a role in SE. However, the data are weakened by the heterogeneity of the reports, descriptive nature and the common divergence from the current recommendations for the treatment of SE. In the study by Hofler et al., success rate in patients with SE receiving lacosamide as first or second drug was 100% (8 of 8), as third drug 81% (11 of 15) and as fourth or later drug was 75% (6 of 8). A retrospective multicenter case series reports administration of IV lacosamide in 39 patients with predominantly partial forms of SE after failure of standard treatment. Lacosamide was the last anticonvulsant in 17 patients, suggesting a success rate of 44%. Albers and colleagues reported termination of SE with lacosamide in seven patients who were unsuccessfully treated with other AEDs before lacosamide. In a recent study, nine patients received lacosamide after failure of at least two other agents, none of them responded to lacosamide according to the predefined criteria. Intravenous levetiracetam seems an efficient and safe AED after failure of benzodiazepines in SE and RSE and IV lacosamide may become a reasonable adjunct in SE, but further clinical experience is required.

Emerging Therapies in Refractory Status Epilepticus

In most patients, the above suggested treatment regimens are sufficient to control the seizures. If the seizures persist even after 24 hours in spite of institution of the above treatment protocols, other treatment strategies may be required to terminate the status. This stage is considered to be super-RSE. Super-RSE is defined as SE that continues or recurs 24 hours or more after the onset of anesthetic therapy, including those cases that recur on the reduction or withdrawal of anesthesia.

Inhalational Anesthetic Agents

Inhalational anesthetic agents (IAs), isoflurane and desflurane are an alternative approach to the treatment of RSE. Their attractive features include efficacy, rapid onset of action and the ability to titrate the dose according to the effects demonstrated on the EEG. Isoflurane and desflurane in enthalial concentrations of 1.2–5% achieved an EEG burst suppression and termination of seizure activity within minutes. However, further studies are needed in this field.

Ketamine

N-methyl-D-aspartate receptor antagonists are candidate drugs for SE that is refractory to drugs modulating GABA receptors. Ketamine is an NMDA receptor antagonist. An experimental study has demonstrated synergistic action of diazepam and ketamine in terminating SE, and suggested that this combination might be a clinically useful therapeutic option for RSE. The efficacy of ketamine in extremely RSE has been documented both in adults and children. It has no cardiac depressant properties, and does not cause hypotension.

Steroids and Immunotherapy

The rationale for the use of steroids and immunotherapy include: the recognition that RSE may be due to antibodies directed against neural elements; increasing recognition of the role of inflammation in epileptogenesis; and SE may be the initial presenting feature of some of the immune-mediated encephalopathies.

Nonpharmacological Treatments

These include resective surgery, ketogenic diet, vagal nerve stimulation, hypothermia and electroconvulsive therapy. Neurosurgical interventions can be an option in patients with extremely RSE if a

no significant differences among the other agents, phenobarbital and diazepam/phenytoin. Prehospital treatment of SE trial demonstrated a clear benefit of active treatment with lorazepam in terminating generalized CSE. Benzodiazepines, lorazepam and diazepam are effective in terminating seizures in 59–78% of patients.

Second Stage or Established Convulsive Status Epilepticus (20–60 Minutes)

When benzodiazepines fail to terminate CSE, a second-line drug, IV phenytoin/osophenytin, phenobarburate or valproate sodium, is considered. Phenytoin is preferred to phenytoin because of its water solubility and neutral pH, thereby allowing more rapid administration with less adverse effects and its compatibility with all IV fluids. Valproate sodium has been shown to be as effective as phenytoin/osophenytin in terminating SE in patients who have previously failed with benzodiazepines as first-line treatment. It would be the best choice in patients with a history of primary generalized epilepsy.

Refractory Status Epilepticus (> 60 Minutes)

Till date, no randomized controlled trials have been done in RSE. Most experience is with continuous infusion (CIv) of anesthetic agents: phenobarbital, midazolam and propofol. No difference was found in mortality among the groups treated with these agents. Pentobarbital was associated with a lower frequency of acute treatment failures and breakthrough seizures. Superior pharmacokinetics and favorable adverse effect profile makes propofol preferred drug in RSE in both adults and children. Refractory status epilepticus was successfully treated with propofol in about two-thirds of patients. Midazolam is an effective, short-acting benzodiazepine that when given as an infusion has an efficacy in RSE. As pentobarbital is not freely available in India, thiopental can be used. Dosing of CIv anesthetic agents for RSE should be titrated to cessation of electrographic seizures or burst suppression. A period of 24–48 hours of electrographic control by cEEG monitoring is recommended prior to slow withdrawal of CIv anesthetic agents for RSE. Use of CIv anesthetic agents frequently requires assisted ventilation and cardiovascular monitoring. Vasopressor agents may also be required to overcome hypotension and cardiopulmonary depression related to these agents.

Newer Antiepileptic Drugs

Newer AEDs have better safety profile and minimal pharmacokinetic interactions with other comedications, which are invariable in patients with critical illness and SE. Though the use of newer AEDs in the treatment of RSE has not been studied systematically, there is cumulative data of their efficacy in both SE and RSE. Three adult reports totaling 10 patients described control of RSE with nasogastric toprimate. Levetiracetam has a different mechanism of action compared to all other AEDs, and may be associated with cellular targets, synaptic vesicular protein 2A (SV2A). Studies using IV levetiracetam in SE, NCSE and RSE in children, adults and elderly suggest the efficacy and safety of the drug. In four studies, all from Germany, treatment with IV levetiracetam showed an overall response in two of three patients with SE. A retrospective study suggests that IV levetiracetam might be an alternative treatment of SE, especially in elderly patients with vascular SE and concomitant medical condition. Its efficacy has also been proved in RSE in patients with brain tumors. In a comparative study of phenytoin, valproate and levetiracetam as second-line drugs in SE, even without significant differences on outcome at discharge, levetiracetam seems less efficient than valproate to control SE after benzodiazepine.
**Neurology**

**focal area of ictal onset can be identified.**

**Maintenance Treatment**

In parallel with emergency treatment, attention must be given to maintenance AED therapy to prevent recurrence of seizures. In patients known to have epilepsy, their usual AEDs should be maintained and dose adjustments made depending on AED levels. In patients presenting de novo, the AEDs, phenytoin/fosphenytoin or valproic acid, used to control the status can in principle be continued as oral maintenance therapy. In others, unless relatively short-lived treatment is anticipated, the preference is to initiate oral maintenance therapy with valproic acid or carbamazepine or any of the newer AEDs topiramate or levetiracetam at standard doses.

**REFERENCES**


3. Lowenstein DH, Bleck T, MacDonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40:120-2.


7. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and treatment with valproic acid or carbamazepine or any of the newer valproic acid, used to control the status can in principle be continued in patients presenting de novo, the AEDs, phenytoin/fosphenytoin or valproic acid, used to control the status can in principle be continued.


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