REVIEW ARTICLE

# STATUS EPILEPTICUS: A REVIEW

*B. Adibeik MD*

**Abstract**

**Objective**

Status Epilepticus (SE) has been described as a series of major motor seizure without recovery of consciousness between seizures.

SE is a medical emergency that requires prompt diagnosis and appropriate treatment.

In this article we shall conclude history, epidemiology, etiology, risk factors, the best management as well as the prognosis of the condition.

**Keywords:** Status Epilepticus (SE), adults, children, neonates.

## Introduction

Status Epilepticus (SE) is a condition manifested with frequent seizures without recovering consciousness in between or is so prolonged that it can lead to a fixed and lasting condition in a comatose or confused state. Although any type of seizure can be presented as SE, the most common form is convulsive generalized Tonic-Clonic Status Epilepticus (GTCSE) which is characterized by repeated generalized seizures, without gaining consciousness or by confusion for few hours or days(1). SE is a medical emergency that requires prompt diagnosis and appropriate treatment. In children GTCSE may be continuous and can lead to systemic cardiovascular dysfunction such as tachycardia, bradycardia and cardiac arrhythmia secondary to hyperkalemia. Using Phenobarbital and phenytoin or their metabolites may cause cardiac arrhythmia or hypotension. There may be respiratory failure either due to status epilepticus or use of Phenobarbital and benzodiazepines at times, altered lymph flew may induce pulmonary edema and renal failure secondary to rhabdomyolysis & myoglobinuria.

Other metabolic complications such as respiratory & metabolic acidosis, anoxia hyponatremia, hyperazothemia and hyperglycemia followed by hypoglycemia may occur.

Autonomic storm causing hyperpyrexia, profuse sweating, salivary and tracheo-bronchial hypersecretion, cerebral complication, hyperthermia, cerebral edema, raised intracranial pressure, neuronal damage & cortical vein thrombosis.

Endocrine abnormalities like elevation of prolactine GH(Growth Hormone) & ACT H(Adrenocorticothropic Hormone) may be seen. There may be pleocytosis of CSF attributable to SE.

Treatment of convulsive status epilepticus can be divided into three steps:

1. Support of respiration and blood pressure and prevention of systemic

Professor of Neurology, Shahid Beheshti Medical University

**Corresponding Author:**
B. Adibeik MD
Tel: +98 21 88050406
Email:kh857654@yahoo.com

complications.
2. Treatment of seizure activity and prevention of seizure recurrence.
3. Identification of etiology and the precipitating factors that lead to SE.
The first step in support is to check the airway and cardiac output.
The patient should be positioned on his side with head down slightly to promote drainage of secretion & prevent aspiration; a soft object being placed beneath the head, helps to prevent injury.

## History

Calmeil (1824) first used the expression eta demal (Status Epilepticus), which at present is called Generalized Tonic-Clonic Epilepticus (GTCSE); it occurs in rapid succession without recovery between convulsions. SE is relatively more frequent in infants and young children, it is seen within the first year of life in about 30% of cases and before the age of 3 in 60%-70% of cases (1).
The seizures are mostly generalized. In fact under the age of 4 years, they are secondarily generalized or purely unilateral and can shift from side to side in the course of the same episode.
The tonic form of SE is an infrequent, erratic motor seizure observed only in newborns. SE is the first manifestation of epilepsy in three-fourths of cases. 50% of cases occur followed by acute brain injury such as meningitis encephalitis, severe dehydration, metabolic disorders, acute anoxic injury in children with cerebral palsy and non-progressive chronic encephalopathy(2).

## Epidemiology

SE occurrence ranges from 1.3 to 6.6% of epileptics, manifesting usually as symptomatic epilepsy. Precipitants could be anti-epileptic withdrawal and/or non-compliance, anti-epileptic interaction and resistance, trauma, hormonal change, emotional stress, progressive cerebral disease, sleep deprivation and febrile illness. Approximately 1% of patients with epilepsy will have an episode of SE in any given year (3).

## Causes and Mechanism

Any brain injury or infection, structural or metabolic derangements, toxicity or chronic epilepsy may trigger SE.
Several mechanisms that terminate seizures, have been postulated. In children, the most common causes of SE are febrile convulsion. Meningitis, encephalitis, birth injury and degenerative neurological disorders due to seizures are common with any cortical lesion; in fact it is postulated that any defect in the mechanisms that terminate seizures, contributes to SE. One of the mechanisms in terminating seizures is the failure of astrocytes to regulate extra cellular K+. There could also be a deficit of γ-aminobutiric acid (GABA) inhibition. After a seizure depolarizing neurons cause increase in extra cellular K+. Astrocytes buffer extra cellular K+ via sodium potassium ATPase. And sodium –potassium ATPase lowers extra cellular K+ by increasing intracellular K+ within glia.
Normally after a seizure, sodium potassium ATPase's activity increases; however after brain injury reduced, sodium potassium ATPase's activity, rendering glia less able to manage the accumulation of extra cellular K+. For the GABA mechanism, it is well established that GABA receptor, modulates the inhibitory chloride channel. Activation of the GABA receptor increases the movement of the chloride in to the neuron causing hyper polarization of the membrane, thus making the neuron less susceptible to activation.
Proconvulsant agents which block or inhibit the GABA receptor, decrease chloride influx and move the resting membrane closer to activation. Prolonged seizures cause functional changes in the GABA receptors, rendering them progressively less sensitive to GABA and benzodiazepine over time. Excitoxicity plays a definite role in SE induced neuronal death. Glutamate receptors are heavily distributed in the hypocampus. Repetitive seizures and SE cause an increased release of Glutamate at presynaptic terminals which in turn produce selective post synaptic neuronal death. With activation of post-synaptic NMDA an AMP A-kainite receptor increase sodium calcium influx into neurons which results in a swelling of the cytoplasm and cytoplasmic organelles especially mitochondria; the neuronal nitric oxide syntethase is activated, resulting in excessive production of nitrous oxide, which in turn generates free radicals that damage cellular proteins(4).

### Risk factors

- History of SE
- Structural or metabolic insult
- Drug interaction
- Lack of compliance
- Medication withdrawal, AEDs, Hypnotic, BZD, sedative
- Infection and autoimmune diseases
- Sleep deprivation and physical / emotional stress

### Prognosis

Mortality ranges from 10-50% and increases with age.

### Poor prognostic factors

- Advanced age
- Duration of SE
- Anoxia
- Stroke
- Central Nervous System infection
- Severe metabolic derangements
- Hypotension
- Renal and Hepatic failure
- Drug toxicity
- Intracranial Hypertension

### Symptoms and signs

Status Epilepticus has been described as a series of major motor seizures without recovery of consciousness between seizures. This fails to include many cases of focal and non-convulsive status and the majority of cases in infants. There is no general agreement on the duration of seizures sufficient to produce this fixed and prolonged condition. SE may occur de novo but also may be associated with clinical and/or neurological conditions like acute bacterial meningitis, encephalitis, intracranial abscess, intracranial tumor or metastasis, stroke, arteriovenous or cavernous malformation. Also hypoglycemia, hyperglycemia, hyponatremia, acute intermittent porphyria, drugs or alcohol abuse or withdrawal, change of anti-epileptic drugs, preeclampsy, use of intravenous contrast agents or electroconvulsive therapy, and lastly idiopathic have been implicated in causing SE. Needless to say that for each of the above mentioned conditions, the approach for management and therapeutic interventions are different.

Any lapse or delay in aggressive control of seizure activity is associated with high morbidity and morality. Thus rapid termination of seizures with simultaneous treatment of underlying illness is of utmost priority in the handling of TCSE patients. SE, lasting one hour or more, increases morbidity tenfold. Furthermore, although very rare, death may be a consequence of SE, soon after acute presentation.

Neurogenic pulmonary edema or life threatening cardiac arrhythmia and more likely prolonged apnea, anoxia may result persistent coma or death.

As stated above, concurrent destructive lesions of brain are common in adult SE and thus, in most, are responsible for morbidity and mortality. As estimated 125000 to 195000 episodes of SE occur in the USA annually, resulting in 22000 to 42000 deaths. Despite its improvement in medical management the incidence of morbidity and mortality still remain high.

For prevention of aspiration during transportation of patients with frequent seizure, the patient should have a nasogastric tube and the stomach contents must be suctioned before transfer. Any injuries sustained during seizures are a result of neglect in the immediate care given following a generalized seizure.

An evaluation must be made for post ictal injuries like humeral neck, femoral trochanter, clavicule and ankle fracture.

Fractures unrelated to seizure are 6 times greater in epileptics than in the general population especially between the ages of 45-64(2,3,4).

Serious head injuries like depressed fracture, intracerebral hemorrhage, subdural hematoma, epidural hematoma and aspiration during seizure should also be considered.

In patients with repetitive seizures or continuous clinical or electrical seizure activity with incomplete neurological recovery interictally for a period of at least 30 minutes, status epilepticus must be considered and the patient should be treated accordingly.

The best way for preventing morbidity and mortality in any patient having continuous seizure for 10 minutes or longer is to treat him/her for SE; in addition, impending SE should be suspected in patients experiencing three or more T-C seizure within a 24 hour period, particularly when this represents an increase from the typical frequency. SE is classified as a generalized or partial

(focal), convulsive and non-convulsive in adults; the most common type of SE is secondary generalized convulsive status (GCSE), which if prolonged, gives way to increasing subtle clinical manifestations. Occasionally subtle SE occurs without prior convulsive activity in a patient with severe diffuse cerebral dysfunction. Acute CNS insult such as anoxia, head injury, stroke, neoplasm and infection account for 50% of cases.

Convulsive status epilepticus can be divided into four major categories and nonconvulsive status epilepticus can be further divided into complex partial and absence types (Figure.1).

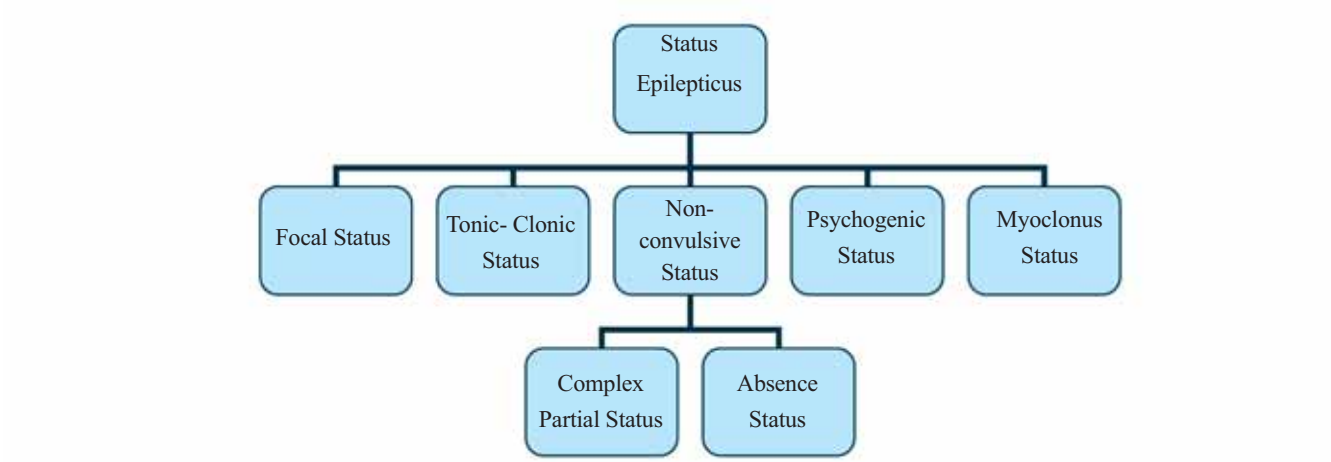


**Fig 1:** Classification of status epilepticus (Wijdicks, 2000:56)

In children most common precipitants are fever and infection, whereas cerebovascular disease is more prominent in older adults. Approximately 20% of all SE cases occur in epileptic patients during medication adjustment or noncompliance; in one third of patients, the cause of SE remains undetermined.SE should be suspected in patient with unexplained coma, with or without motor manifestations. Non-epileptic phenomena, including tremors, myoclonic and nystagmoid eye movement, oral or buccal movements frequently occur following anoxia, brain stem or bilateral cerebral ischemia. Severe metabolic and electrolyte disturbances may be difficult to differentiate clinically from non convulsive status epilepticus. Occasionally prolonged psychogenic seizure are misinterpreted and treated as SE.

## Status Epilepticus in Neonates

Neonatal SE has been defined by Dreyfus-Brisac & Monod (1964) as the repetition of clinical or even sub clinical seizures which occur for at least a few hours. Its recognition poses major difficulties in infants as stated by Dreyfus-Brisac & Monod (5,6). The seizures are clonic episodes with limited distribution. There may be tonic episodes with posturing and rotation of head and eyes. Eye opening, blinking and nystagmous, abnormal crying and vasomotor changes other rhythmic movements of extremities, random myoclonic movements, organized movements such as peddling or stepping and repetitive facial movements may not be suggested as a seizure for a physician who does not know the ropes. Additional problems are the frequent occurrence of epileptiform activity on the EEG without clinical manifestations and often an obtunded or comatose state of the child at most risk for seizure. For this reason, Aicardi & Chevire (1970) recommended listing recurrent neonatal seizures as serial seizure and not true SE. It should be noted that EEGs are essential in diagnosing SE in the newborns. There may be a slow spike and wave pattern or rhythmic alpha like discharges; a variety of different patterns may be seen on the same recording. These discharges are almost invariably focal with only rare generalized or bilaterally synchronous discharges. The supportive care

for a neonate with SE is similar to that given to the older child.

SE in infancy is almost always due to an acute encephalopathy. Glucose, Calcium and electrolytes should always be checked. Asphyxia is apparent from the history and initial examination. Most of these infants require a lumbar puncture to rule out acute meningitis. If the etiology is not otherwise apparent, metabolic screening, toxicology and neuro-imaging for congenital malformations are essential. In addition the child should receive 100 mg pyridoxine intravenously, best given with EEG monitoring. This should result in prompt normalizing of the EEG if the infant has pyridoxine deficiency or dependency(7).

Therapy of neonatal SE depends initially on diagnosis. Phenobarbital is the drug of choice for stopping neonatal seizures with serum concentration of 40 µg/ml. With this approach, 77% of seizures are controlled. If Phenobarbital is not successful, phenytoin is used as a second drug with 20 mg/kg loading dose and maintenance of 4-5 mg/kg/day must be given IV since drug is not absorbed consistently from the neonatal GI tract. If neither of these drugs are effective, other agents to consider include Benzodiazepine, Primidone and Sodium Valporate. The prognosis for neonatal SE is guarded due to underlying etiologies.

## Differential Diagnosis of Status Epilepticus

### I. Convulsive status epilepticus

Generalized Convulsive Status Epilepticus (GCSE) can be seen in psychogenic seizures and unusual presentation of movement disorders (Myoclonus, Tremor and Chorea)(8).

1. Psychogenic spells can be extremely difficult to distinguish from epileptic seizures and there are many case reports of unnecessary intubation and medication induced coma. Even an experienced Epilepsy specialist may need to use video-EEG monitoring.

2. Movement disorders, not affecting consciousness, although a number of diseases can cause both movement disorder and seizures; for example Creutzfeld Jacob disease (CJD). Hyperactive reflexes and sustained posture, seen in stroke and hypoxia victims, can resemble seizures, as can hypocalcemic tetany.

### II. Non convulsive status epilepticus

Basically the differential form of altered mental status includes

1. Trauma: Concussion, Intracranial hemorrhage, Intracranial Hypertension
2. Infectious: Meningo-encephalitis
3. Toxic: Drug overdose, poisoning
4. Metabolic: Electrolytes'abnormalities(especia lly hypernatremia), hypoglycemia, hypoxia, hypercarbia
5. Organ failure: Liver failure, respiratory failure, renal and cardiac failure, thyroid and adrenal disorders
6. Psychiatric: Fuge states, psychogenic spells, malingering
7. Others: Cerebral Vasculitis

## Management of Status Epilepticus

**Step I)** Assess Airway, Breathing and Circulation

- Administer O2, Monitor Cardiac rhythm, O2 saturation and vital signs
- Bedside glucose test
- Draw blood for AEDs , Hematologic chemistries, toxicological screens, Establish intravenous line with normal saline
- Thiamine 100mg and dextrose (50%) 50ml intravenous (DW 25% 2ml/kg in children)
- Obtain history and perform examination

**Step II)** Administer intravenous Diazepam 0.25 mg/kg in adults,0.1mg/kg in children) (Up to 5 mg/min) or Lorazepam (0.1mg/kg in adults, 0.05- 0.5 mg/kg in children) (up to 2 mg/min) repeat once if seizures persist.

Simultaneous administration of phenytoin 20 mg/kg load (up to 50 mg/min in adults and 1 mg/kg/min in children or patient< 50 kg) or Fosphenytoin 15-20 mg/kg (up to 150 mg/min) if seizure persists give PHT 5 mg/kg up to 30 mg/kg to level of 30 µg/ml)

**Step III)** Intubate, place arterial line and draw ABGs

- Phenobarbital 20 mg/kg loading with the rate of 50-100 mg/kg/min in children.
- Generalized anesthesia with Midazolam 0.2 mg/kg loading dose followed by infusion at 0.1-0.4 mg/kg/hr or Propofol 2 mg/kg/hr.

**Step IV)** If seizures persist, consider pharmacological coma with Pentobarbital 5-8 mg/kg loading, followed by maintenance 2-4 mg/ kg/hr titrated to burst suppressive for 6-48 hours (Pentobarbital level 24-45 µg/ml)(9).

Treatment Protocol for SE with PENTOBARBITAL COMA (Setting ICU, Intubation, EEG monitoring): Nonconvulsive SE when documented by EEG can be controlled under electro-encephalographic monitoring with Benzodiazepine (10,11). The management of SE in patient with pre-eclampsia is notably different. The management of Generalized Tonic-Clonic Status Epilepticus is presented in Table 1 and figure 2.

**Table 1:** Management of Generalized Tonic-Clonic Status Epilepticus in children ( 12,13,14)

| Time from start of treatment | Procedure |
|---|---|
| **0 minutes** | • Verify diagnosis of Status epilepticus. Monitor cardio respiratory function. ECG, pulse oximetry, and stabilize. EEG if possible. Insert oral airway, administer oxygen if needed, Insert i.v. catheter with normal saline solution. Draw AED levels, glucose, electrolytes, calcium, magnesium, BUN, CBC, arterial blood gas. |
| **5 minutes** | • Start i.v. normal saline solution. Administer 50% glucose at 2 ml/kg. |
| **10-30 minutes** | • i.v. lorazepam, 0.1 mg/kg, at 1-2 mg/min to maximum of 5 mg. Start i.v. fosphenytoin 20 mg kg infused at 150 mg/min (or i.v. phenytoin 18-20 mg/kg, at a rate not to exceed 1 mg/kg per minute or 50/mg/min) with ECG and blood pressure monitoring; additional 10 mg/kg may be given after ward monitoring. |
| **31-60 minutes** | • If seizures persist, administer i.v. Phenobarbital at a rate not to exceed 50 mg/min until seizures stop or to a loading dose of 20 mg/kg. |
| **>60 minutes** | • If seizures persist, options include: (1) i.v. diazepam- continuous infusion, 50 mg diluted in 250 ml normal saline solution or D5W at 1 ml/kg/hour (2mg/kg/hour) to achieve blood levels of 0.2-0.8 mg/ml. (2) i.v. pentobarbital – initial loading dose of 5 mg/kg followed by maintenance infusion of 1-3 mg/kg/hour (with EEG monitoring) to produce burst suppression pattern on EEG. Decrease infusion rate 4-6 hours later to check for reappearance of seizures. If seen, repeat procedure. If not, taper over 12- 24 hours.<br>• If seizures are not controlled, ask an anesthesiologist to institute general anesthesia ith halothane and neuromuscular blockade. |

ECG: electrocardiogram
EEG: electroencephalography
i.v.: intravenous
AED: antiepileptic drug
BUN: blood urea nitrogen
CBC: complete blood cell count
PE: phenytoin
D5W: 5% dextrose in water

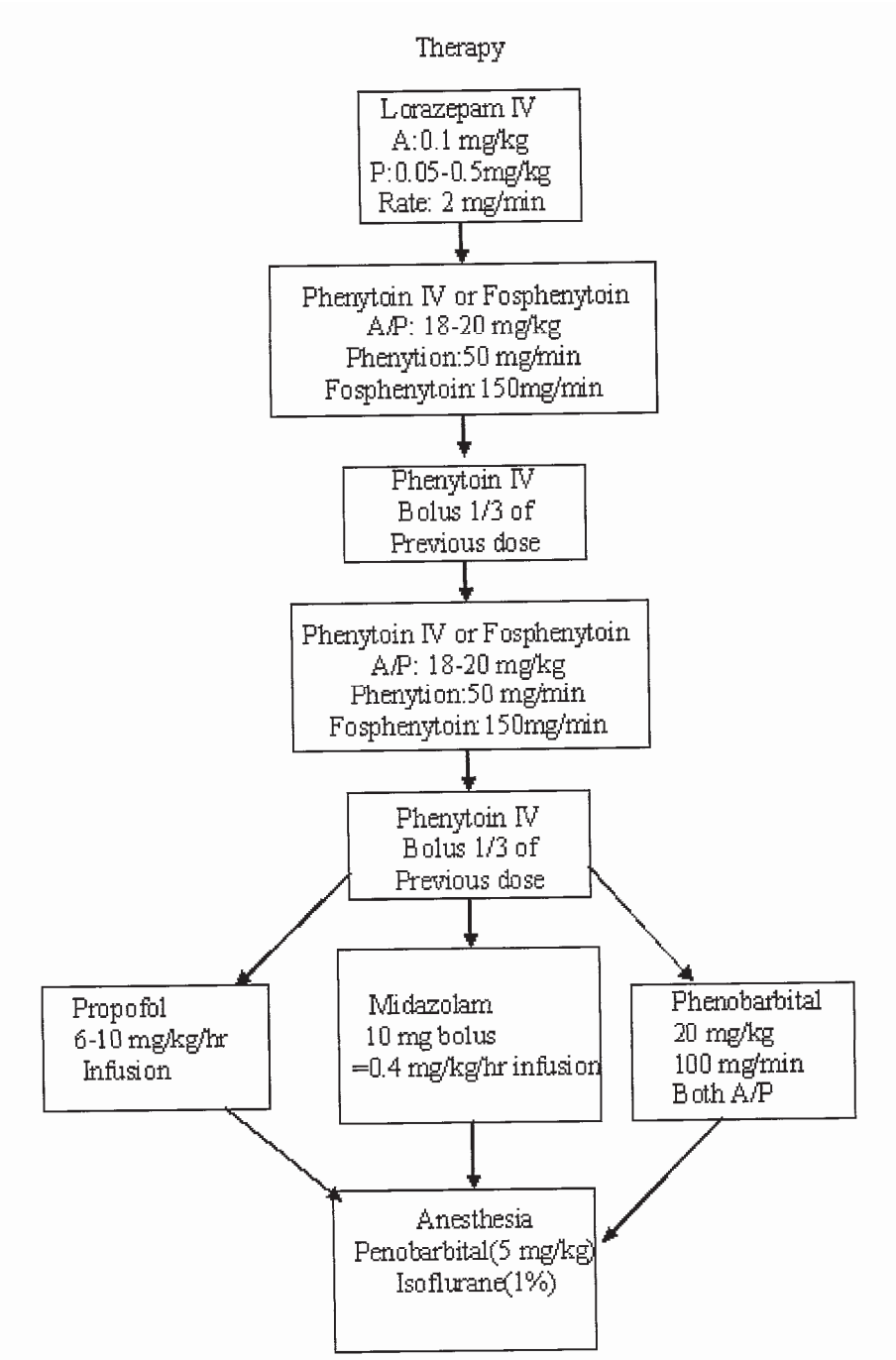


**Fig 2:** Algorithm for management of convulsive status epilepticus

A: adult dose
BP: Blood pressure
IMV: Intermittent mandatory ventilation
IV: intravenous
P: Pediatric dose
WBC: White blood cells

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