

# Update on the management of status epilepticus

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## Abstract

Status epilepticus (SE) is widely recognized as the second most common and life-threatening neurological emergency after stroke, which carries a high mortality and morbidity. The main goal of treatment is to emergently stop clinical and electrographic seizure activity. Most authorities agree on three-line treatment for SE with administration of benzodiazepines followed by longer-acting anti-epileptic agents and finally, if seizures persist, the administration of general anaesthetic agents.

**Keywords** EEG monitoring; epilepsy; new anti-epileptic medication; refractory status epilepticus; status epilepticus

**Royal college of Anaesthetists CPD Matrix:** 2F00; 3F00

## Introduction

Status epilepticus (SE) is widely recognized as the second-most common and life-threatening neurological emergency after stroke, which carry a high mortality and morbidity. Its annual incidence is 10–41 per 100,000 people. SE definition has recently changed and keeps doing so as new evidence emerges. SE was defined as continuous seizure activity lasting longer than 5 minutes. Recently, SE have been re-defined depending upon the classification as whether this was convulsive (CSE), focal (FSE) or absent status epilepticus (ASE) with different timelines defined with respectively 5 minutes, 10 minutes and 10–15 minutes for absent status epilepticus. This new definition was considering the evidence that after these timelines the seizure activity was unlikely to stop spontaneously and therefore the need to aggressively treat such complex pathology. The importance of this new definition is related with the type of seizure, as the time after which a patient has long-term consequences vary.

## Classification of SE

SE is defined as time after which if seizures do not terminate patient is considered in SE and therefore the initial therapy phase as to commence. The timeline is different as the patient is in a state of *convulsive status epilepticus* (CSE) (5 minutes), focal status epilepticus with impaired consciousness (10 minutes) and absent status epilepticus (10–15 minutes) generally known as

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## Learning objectives

After reading this article, you should understand:

- the new classification and aetiology of status epilepticus
- the new guideline on drugs used in the treatment of status epilepticus
- the future directions on treatment of status epilepticus

*non-convulsive SE* (NCSE). This new classification is important because the time after which the ongoing seizures have long-term consequences differ. CSE has consequences as permanent neuronal damage after 30 minutes of its onset. NCSE or FSE with impaired consciousness have consequences after 60 minutes while absent SE timelines as to permanent consequences is unknown. Seizure activity that persists after first-line treatment (benzodiazepines has become a standard of care for early status epilepticus) is defined as established status epilepticus (ESE) and widely treated with second-line medications. SE that persists after a first-line and second-line agents is defined as refractory status epilepticus (RSE). Super refractory status epilepticus (SRSE) is defined as continuous seizure activity despite anaesthetic therapy or recurrence of seizure upon withdrawal of anaesthetic therapy.

## Aetiology of SE

SE is a dynamic entity and its pathophysiology is still poorly understood. SE is often a manifestation of pre-existing epilepsy and the main causes are low blood concentrations of antiepileptic drugs in patients with chronic epilepsy (34%), or consequence of multitude cerebral insults such as remote symptomatic causes (24%), cerebrovascular accidents (22%), anoxia or hypoxia (~10%), metabolic causes (~10%), and alcohol and drug withdrawal (~10%) (see [Box 1](#)).

## Complications of SE

### Central nervous system

Seizure activity results in sympathetic stimulation leading to an increase in cerebral blood flow and blood glucose levels. This initially meets the needs of the increased metabolic demand of neurones; however, as seizures continue, these compensatory mechanisms become exhausted; anaerobic metabolism intervenes and results in cerebral hypoxia and neuronal damage. The safeguarding of homeostasis is essential for the prevention of neuronal injury, and maximizing the supply of oxygen and glucose to the brain, by maintaining cerebral blood flow and blood gases, is as essential as reducing cerebral metabolic needs by restricting seizures and hyperthermia.

### Systemic effects

Systemic effects are related to a massive catecholamine release and hyper adrenergic state that may result in neuro-cardiogenic, pulmonary and, sometimes, musculoskeletal or renal injury (see [Box 2](#)).

### Aetiology of status epilepticus

- New manifestation of epilepsy
- Cerebrovascular diseases
- CNS infection
- Neurodegenerative diseases
- Intracranial tumours
- Cortical dysplasia
- Head trauma
- Alcohol withdrawal or chronic consumption
- Intoxication
- Withdrawal or low level AED
- Cerebral hypoxia or anoxia
- Metabolic disturbances (e.g. electrolyte imbalances, glucose imbalances, organ failure, acidosis, renal failure, hepatic encephalopathy, etc.)
- Autoimmune disorder
- Mitochondrial diseases
- Chromosomal aberrations and genetic anomalies
- Neurocutaneous syndrome
- Metabolic disorders
- Others (Malignant hyperpyrexia, eclampsia, sepsis etc)

#### Box 1

### Complications of status epilepticus

#### Central nervous system

- Cerebral oedema
- Cerebral venous thrombosis
- Cerebral hypoxia
- Cerebral haemorrhage

#### Cardiovascular

- Hyper/hypotension
- Cardiac arrest
- Cardiogenic shock
- Myocardial infarction
- Arrhythmias

#### Respiratory

- Pulmonary oedema
- Respiratory failure

#### Metabolic

- Hyponatraemia
- Hyperkalaemia
- Hypoglycaemia
- Metabolic acidosis

#### Other

- Rhabdomyolysis
- Fractures
- Acute tubular necrosis

#### Box 2

### Emergency management of SE

Management of SE consists of:

- resuscitation and diagnostic evaluation
- rapid termination of seizures
- treatment of life-threatening underlying cause.

The main goal of treatment is to emergently stop clinical and electrographic seizure activity. Most seizure activities self-terminate within 5 minutes, therefore the initial treatment strategy consists in stabilizing the patient while assessing and managing airway, breathing, and circulation, administering oxygen, gaining intravenous (IV) access and monitoring cardiac activity. If the patient needs respiratory assistance, perform tracheal intubation when necessary. Along with resuscitation, a diagnostic work-up is necessary with finger stick glucose, electrolyte, haematology, toxicology screen and anticonvulsant levels. Lumbar puncture can be performed if appropriate clinical picture is suspected once the patient is stabilized.

Owing to lack of well-conducted and appropriately powered randomized controlled studies, protocols of treatment of SE have remained almost unchanged, despite promising results in pre-clinical animal models and some human trials for newer drugs.

Most authorities agree on three-line treatment for SE.

**Initial therapy phase (First line treatment):** a benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given their demonstrated efficacy, safety and tolerability. Compared to previous guideline, IV phenobarbital it is now established as efficacious and well tolerated as initial therapy.

**Established status epilepticus SE (Second line treatment):** Patients who respond to benzodiazepine therapy are started on longer acting anti-epileptic drugs (AED) to prevent the re-emergence of further seizures following benzodiazepine therapy. Similarly, those patients who do not respond, and those patients which seizure activity persist after initial therapy phase, are given AEDs to try and control their SE. However, there is only a 7% chance that continuing SE will respond to second line treatment. Treatment for established status epilepticus includes, phenytoin, fosphenytoin, valproic acid and levetiracetam. Most of the recent effort and advances of medications for SE are concentrating on new drugs able to be effective in established status epilepticus, when initial therapy phase with benzodiazepine fail. Seizure activity that persist after first and second line treatment are considered to be in refractory status epilepticus (see Box 3).

**Refractory status epilepticus RSE (Third line treatment):** is defined as the persistence of seizure activity, or failure to respond to first and second line treatments. Intravenous anaesthetic therapy is the standard of care to treat RSE. When RSE is evident, the patient requires transfer to intensive care, with the goal of CEEG monitoring and systemic support with tracheal intubation and cardiovascular support.

Preferred agents used include propofol, thiopental, midazolam and pentobarbital. While on CEEG monitoring, anaesthetic agents are titrated to produce at least 10-seconds EEG burst interval suppression. Usually anaesthetic agents are maintained

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