# What is Status Epilepticus?

## *Definition*

- A number of definitions exist for status epilepticus.

A common definition for convulsive status epilepticus is 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between the seizures.

*This duration was based* on the time required to demonstrate neuronal injury in animal models.

- *If the patient has a prolonged (>5-10 min.) seizure or repetitive (3 or more/hr) seizures without recovery between episodes, he is considered to be in SE and the Rx protocol initiated.*
- The term "prolonged" was previously used to refer to seizures lasting 30 minutes or longer; this interval has been shortened to 5-10 min. for several reasons:

1- almost all convulsive seizures in adults cease in less than 5 minutes without treatment; seizures lasting longer than this are more likely to be self-sustained and to require intervention.

2- . the longer seizures persist, the harder they are to terminate pharmacologically, due to down-regulation of inhibitory GABA receptors.

3- . outcome tends to correlate with seizure duration even after controlling for other important factors, such as age and cause of SE.

- The distinguishing feature between acute repetitive seizures and status epilepticus is the recovery of consciousness in between the episodes of seizures in acute repetitive seizures.
- Seizures may present on a spectrum which extends from isolated brief seizures (<5min.) to acute repetitive seizures (3 or more / hr) to status epilepticus.

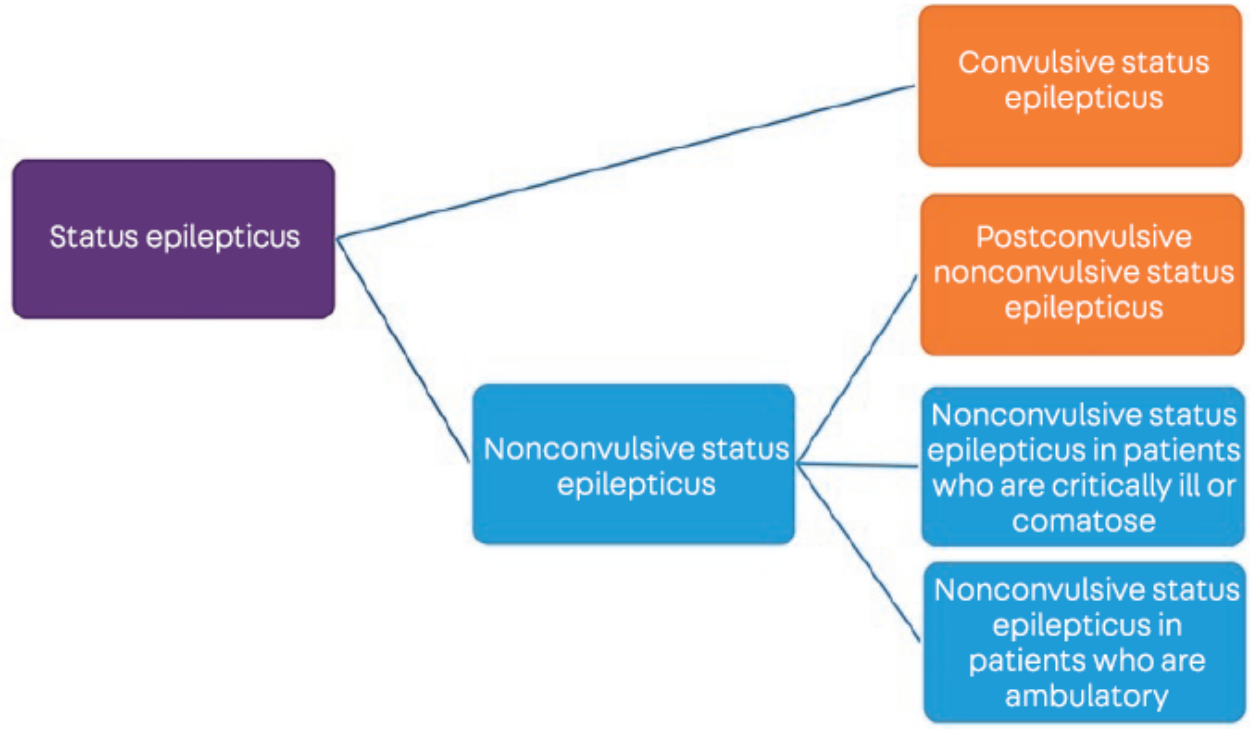


FIGURE 8-1
Simplified clinical framework for status epilepticus. The purple box represents all forms of status epilepticus, which can be subdivided into convulsive status epilepticus and nonconvulsive status epilepticus. It is generally regarded that postconvulsive nonconvulsive status epilepticus should be treated similarly to convulsive status epilepticus (in orange boxes). Blue boxes represent more controversial treatment paradigms for nonconvulsive status epilepticus in patients who are critically ill and in patients who are ambulatory.

## *Epidemiology*

- The annual incidence of Generalised tonic-clonic convulsive SE is estimated to be 18–28 cases per 100 000 persons.
- Acute seizures account for 1% of adult and 2% of pediatric emergency department visits– 6% of these are in SE. Higher in developing countries.
- SE occurs most commonly in children, the mentally handicapped, and in those with

structural cerebral pathology especially in the frontal lobes.

- About 5% of all adult patients attending an epilepsy clinic will have at least one episode of status in the course of their epilepsy; in children the proportion is between 10–25% .

## *Causes of SE*

- Most episodes of status develop in patients without a prior history of epilepsy.
- Common causes are cerebral infection, trauma, cerebrovascular disease, cerebral tumor, acute toxic or metabolic disturbances, or anoxic encephalopathy. ***This group of patients have a worse outcome, than patients with pre-existing epilepsy.***
- In patients with pre-existing epilepsy, status can be precipitated by drug withdrawal, intercurrent illness or metabolic disturbance, or the progression of the underlying disease, and is more common in symptomatic than in idiopathic epilepsy.

Stages of SE

| | |
|---|---|
| **Premonitory SE** | Increased frequency or severity of seizures over hours to days, can be a warning of impending SE |
| **Early SE** | Up to 30 minutes continuous seizures (or recurrent seizures with no recovery between) |
| **Established SE** | More than 30 minutes continuous seizures |
| **Refractory SE** | More than 30-60 minutes continuous seizures, despite adequate AED treatment |

## *Approach to SE*

The approach to the patient with SE should proceed along four overlapping, often concurrent, lines:

1- terminate SE,

2- prevent its recurrence,

3- treat its complications, and

4- determine and manage its etiology *Refractory SE*

- Irrespective of the timeframe, SE that persists despite adequate administration of benzodiazepines and at least one antiepileptic drug is labelled refractory SE.
- This resistance to treatment occurs in 23–43% of patients with SE.
- Patients with refractory generalized convulsive SE are at high risk to suffer from serious systemic consequences such as tachyarrhythmia, pulmonary oedema, hyperthermia, and rhabdomyolysis and therefore rapid seizure suppression is mandatory.

## *Risk factors for refractory SE*

- Underlying acute brain insult etiology– in particular, acute encephalitis but also stroke, trauma.
- Lack of pre-existing epilepsy.
- focal neurological signs/ seizures at onset.

| Neurocritical Care Society 2012 | | American Epilepsy Society 2016 |
|---|---|---|
| Stabilize patient<br>(Airway, breathing, circulation, disability)<br>Finger-stick glucose<br>IV access and blood work<br>Emergent AED administration:<br>Benzodiazepines<br>IV lorazepam (0.1 mg/kg up to 4 mg)<br>IM midazolam (0.2 mg/kg up to 10 mg)<br>IV diazepam (0.15 mg/kg up to 10 mg) | 0–5 minutes | Stabilize patient<br>(Airway, breathing, circulation, disability)<br>Finger-stick glucose<br>IV access and blood work |
| Urgent AED—5–10 minutes<br>IV fosphenytoin/phenytoin (20 mg/kg)<br>IV valproate sodium (20–40 mg/kg)<br>IV phenobarbital (20 mg/kg)<br>IV levetiracetam (1000–3000 mg)<br>Midazolam infusion | 5–20 minutes | Benzodiazepine administration<br>IM midazolam (10 mg if >40 kg)<br>IV lorazepam (0.1 mg/kg/dose, maximum 4 mg/dose)<br>IV diazepam (0.15–0.2 mg/kg/dose, maximum 10 mg) |

Refractory status epilepticus treatments—20–60 minutes—after second AED
- Midazolam (0.2 mg/kg; infusion rate of 2 mg/min)
- Pentobarbital (5–15 mg/kg, may give an additional 5–10 mg/kg; administer at an infusion rate ≤50 mg/min)
- Propofol (20 mcg/kg/min with 1–2 mg/kg loading dose)
- Thiopental (2–7 mg/kg; administer at an infusion rate ≤50 mg/min)

20–40 minutes

Second AED
- IV fosphenytoin (20 mg/kg, maximum 1500 mg)
- IV valproate sodium (40 mg/kg, maximum 3000 mg/dose)
- IV levetiracetam (60 mg/kg, maximum 4500 mg/dose)
- Or if none are available, IV phenobarbital (15 mg/kg)

40–60 minutes

Third therapy phase
- Repeat second-line therapy or anesthetic doses of thiopental, midazolam, pentobarbital, or propofol with continuous EEG monitoring

**FIGURE 8-2**

**Comparison of treatment algorithms for convulsive status epilepticus from the Neurocritical Care Society and the American Epilepsy Society.**

AED = antiepileptic drug; EEG = electroencephalogram; IM = intramuscular; IV = intravenous.

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## General Management - In Parallel to Drug Management

### General Medical Measures

Secure airway and resuscitate

Administer oxygen

Assess cardiorespiratory function

Establish intravenous access (large veins if possible)

Measure capillary blood glucose and immediately correct hypoglycaemia.
- Give 75 mL 20% glucose intravenously over 5 minutes
- If no intravenous access 1 mg intramuscular glucagon
- Re-check blood glucose after 15 minutes

Check temperature

Check blood gases

If poor nutrition/alcohol abuse suspected give:

Pabrinex® (thiamine, riboflavin, pyridoxine, ascorbic acid, nicotinamide) ONE PAIR intravenously over 10 minutes

**OR**

Thiamine 100 mg intravenously in 100 mL 0.9% sodium chloride over 30 minutes

**If woman of child bearing age—consider pregnancy test**

Take blood for:

| | |
|---|---|
| electrolytes | liver function tests and INR |
| glucose | anti-epileptic drug levels |
| calcium | creatine kinase |
| magnesium | alcohol and toxicology screen |
| full blood count | culture as appropriate |

**CAUTION: Not all seizures are epileptic**

In psychogenic non-epileptic seizures 'pseudostatus' **OR**, treatment with sedation or anti-epileptic drugs is not indicated

Consider urgent EEG and seek senior opinion

## *Investigations to consider after seizures stop*

- Brain imaging– usually a CT scan in the ER. ?MRI/ MRV Brain later.

- LP- mildly raised CSF protein and WBC's (neutrophils) may be caused by the SE itself. Encephalitis– whether viral, autoimmune or paraneoplastic causes a lymphocytic pleocytosis in the CSF

# In-Hospital **Emergency** Drug Management of Convulsive Status Epilepticus in Adults

See page 2 for essential parallel general measures

**STEP 1: benzodiazepine give if fitting for > 5 min**

First choice:

- **Intravenous lorazepam:** Usual dose bolus **2 to 4 mg** (maximum rate 2 mg/min). If necessary repeat up to a total maximum dose of 0.1 mg/kg.

**OR** **Intravenous diazepam:** Usual dose **5 to 10 mg** titrate for effect, up to 20 mg if necessary. Do not gi too fast to avoid respiratory depression (maximum rate 5 mg/min).
Diazepam is rapidly redistributed and may accumulate with repeated dosing.

**OR** **Intravenous clonazepam:** Usual dose 1 mg, if necessary repeat 1 mg dose after 5 minutes (maximum rate 0.5 mg/min).

If intravenous is difficult or not possible:

- **Buccal midazolam:** Usual dose **10 mg** (caution: Give 5 mg in the elderly or patients less than 50 kg Repeat dose once after 10 minutes if necessary.[1]
If buccal preparation not available, use 10 mg/2 mL injection via buccal route.

**OR** **Intramuscular midazolam:** Usual dose 10 mg (Caution: Give 5 mg in the elderly or patients weighin less than 50 kg). Repeat dose once after 10 minutes if necessary.

If intravenous, buccal and intramuscular are not possible:

- **Rectal diazepam:** Usual dose **10 mg** (caution: give 5 mg in elderly patients or patients weighing less than 50 kg). Repeat dose once after 10 minutes if necessary.

If seizures stop, the recurrence rate is high; most patients need an intravenous stage 2 anti-epileptic drug (see below for doses) to prevent further seizures

**STEP 2: f no response to tep 1 WITHIN 10 min, give stage 2 agent and INFORM NEURO-INTENSIVIST or EXPERIENCED ANAESTHETIST**

Second stage antiepileptic drug given **intravenously and inform neurointensivist or experienced anaesthetist**
See loading dose proformas for administration guidance

*If there is no specific contraindication or a clear preference for alternative:*

**Phenytoin**; **18 mg/kg** (range 15–20); **maximum rate 50 mg/min**. Infuse into large or central vein via filter with ECG and blood pressure monitoring (caution **hypotension, bradycardia)**. Check concomitant drugs (phenytoin is an enzyme inducer—its effect on the half-life of affected drugs is not immediate). For patients already on phenytoin, see note on page 2* before administering.

**OR**

**Levetiracetam; 30 mg/kg** (range 20–70); **infuse over 10 minutes**; no interactions; good side effect profile in this setting but comparative efficacy remains to be established; renal excretion.[2,3]

**OR**

**Sodium Valproate; 30 mg/kg** (range 15–30); **infuse over 5 minutes**
Contraindicated in mitochondrial disease. Avoid in status of unknown cause in young people. Caution: in pregnancy or acute liver failure, where an alternative is preferable. Check concomitant drugs (valproate is an enzyme inhibitor, with immediate effect on half-life of affected drugs).[4,5]

**OR**

**Phenobarbital; 10 mg/kg** (range 10–15)**; maximum rate 100 mg/min.** Monitor blood pressure, ECG and respiratory function (Caution: **respiratory depression** may occur—only give if ventilatory support can be provided). Check concomitant drugs (phenobarbital is an enzyme inducer—its effect on the half-life of affected drugs is not immediate).

**STEP 3:**
If no response to step 2 within 30 minutes of onset anaesthesia and ICU admission

**General anaesthesia with intubation and ventilation**

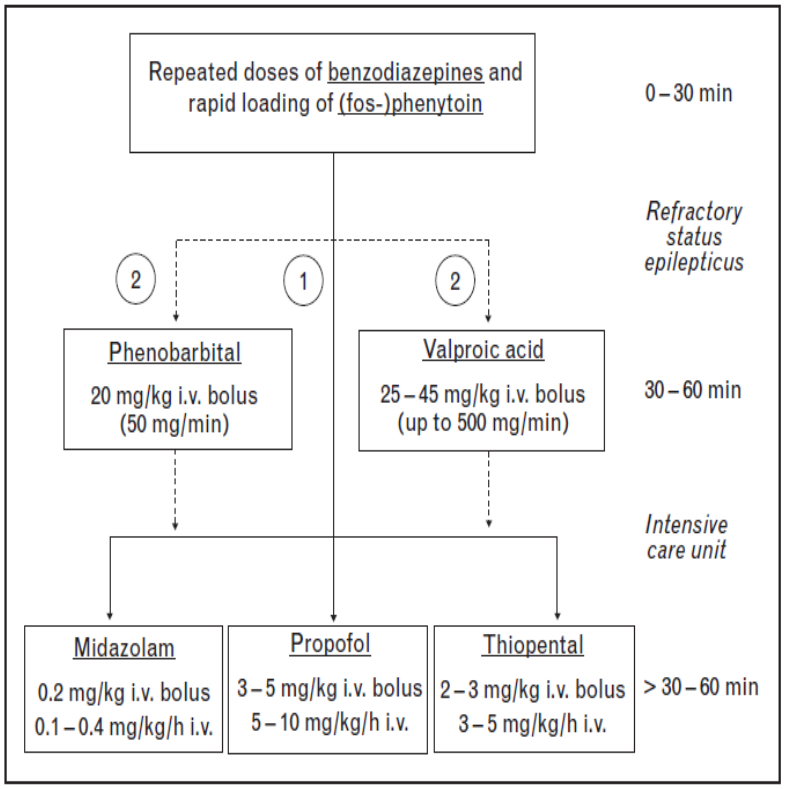
Consider if haemodynamically unstable at any stage or if respiratory support is needed

- These drugs must be **administered by a neurointensivist/experienced anaesthetist in an intensive care unit (ICU) setting** as per local protocols to control clinical/EEG seizures
- *Induction*: usually propofol (1.5–3 mg/kg bolus); caution: hypotension, bradycardia **OR**
  - thiopentone (usually 3–5 mg/kg bolus, additional boluses of 50 mg every 3 minutes until seizures terminated may be given if blood pressure remains stable)
- *Maintenance*: Propofol 1–5 mg/kg/hour titrated to effect; prolonged use may lead to propofol infusion syndrome **OR**
  - midazolam if patient already ventilated, initial bolus 1 mg intravenously and titrate to effect then 0.05–0.20 mg/kg/hour titrated to effect **OR** consider propofol with midazolam **OR**
  - thiopentone 3–5 mg/kg/hour titrated to effect. Caution: hypotension, cardiac suppression, immunosuppression, hypokalaemia, pancreatitis and drug accumulation
- **EEG monitoring is indicated (continuous or minimum every 24 hours) to assess level of anaesthesia and abolition of ictal discharges.**

Over next 24-48 hours, optimise doses and levels of non-anaesthetic anti-epileptic drugs and, if no electrical or clinical evidence of ongoing seizures, withdraw anaesthesia to assess response.

**Figure 1 Treatment algorithm for refractory status epilepticus**

Pharmacological treatment after failure of first and second-line anticonvulsants. In generalized convulsive status epilepticus, rapid administration of intravenous (i.v.) anaesthetics is recommended (treatment pathway 1) but some centres at first prefer a third nonanaesthetic such as phenobarbital or valproic acid before induction of pharmacological coma (treatment pathway 2). In nonconvulsive status epilepticus, pathway 2 is recommended and anaesthetics are preferably avoided.



ICU Management

- Tapering of the maximum dose of anaesthetics is recommended after 12–24 h, aiming to stop Rx by 24-48 hrs.
- Don't forget Rx aimed at the underlying cause of the SE such as antiviral Rx for encephalitis, and Rx of medical complications ,e.g, rhabdomyolysis, cerebral oedema
- If seizure activity recurs on tapering or stopping anaesthetics, this is a grave situation— recently termed "super-refractory SE".
- In this situation, the anaesthetic should be restarted or the dose increased again or a different anaesthetic used or combination Rx is used— usually propofol+midazolam.
- Cycles longer than 24-48 hrs. may be necessary and patients may remain in "super-refractory" SE for weeks.

Problems associated with ICU Rx

- ***Midazolam***: Hypotension .the only benzodiazepine that has pharmacokinetic properties suitable for prolonged infusion without accumulation, but tolerance may occur quite rapidly requiring progressively higher doses and close monitoring for breakthrough seizures
- ***Thiopental***: Hypotension . Exhibit zero order kinetics and due to rapid redistribution have a profound tendency to accumulation resulting in a long half-life in anaesthesia and thus long recovery time . It is not uncommon for anaesthesia to persist for days even after an infusion of only 12 h or so.
- ***Propofol***: Hypotension (less commonly). Propofol infusion syndrome (characterized by cardiac failure, hyperlipidaemia, severe metabolic acidosis, rhabdomyolysis, and renal failure) is rare but may occur with prolonged (>48 h) treatment.
- Hypotension: barbiturates > midazolam > propofol & I.V. fluids.
- Many patients need vasopressor Rx
- Raised ICP

- Infections
- Gastrparesis

Super-refractory (malignant) SE

- SE that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases where SE recurs on the reduction or withdrawal of anaesthesia.
- It is an uncommon but important clinical problem with high mortality and morbidity rates.
- New-Onset Refractory SE (NORSE) has a very aggressive course with very high mortality– underlying encephalitis ( viral or immune-mediated most likely cause, based on CSF lymphocytosis).