Management of Convulsive Status Epilepticus in Adults: A Brief Overview
Convulsive Status Epilepticus: Requires Emergency Intervention

Status epilepticus is associated with multiple complications, including death.

- Neurological Emergency
- Medical Emergency

Overall mortality has been estimated at 9.4%, of whom 93% have persisting seizure activity 60 minutes after initiating treatment. (SENSE Registry 2019)

*Intervene early and aggressively*

Therapeutic delay and under-treatment are recognised as significant factors influencing both morbidity & mortality

Ann Neurol. 2019;85:421-43
Status Epilepticus: Neuro-molecular Changes

_Prolonged status results in failure of endogenous mechanisms which normally terminate seizure activity._

These involve both:

- Loss of endogenous inhibitory mechanisms
- Excessive, abnormal neuronal excitation

These processes, in turn, mean that many _anti-seizure medications become less effective as the duration of the seizure persists_.


Status Epilepticus: Some Neuro-molecular Mechanisms

- **Hyper-excitability**
- **Pharmacoresistance**
- **Neuronal Injury**
- **Poor prognosis**
- **Mortality**

Consequences of Persisting SE

In short, with persisting status, there is a progressive increase in:

- **Excitotoxic neuronal injury**
- **Pharmaco-resistance**

These negatively affect functional outcome and increase mortality

*Ann Neurol. 2019. 85:421-432*
In addition to these molecular mechanisms, there are more overt pathological processes associated with prolonged SE which may have to deal with which include:

- Hypoxia
- Acidosis
- Haemodynamic instability
- Hyper -> hypoglycaemia
- Rhabdomyolysis and hyperkalaemia
Status Epilepticus: Definitions

The definition of Status epilepticus remains constantly under review with an eye to improving its clinical usefulness.
Status Epilepticus
Operational Definition:

SE is now defined as **5 minutes** or more of:

- *Continuous clinical and/or electrographic seizure activity*
- or
- *Recurrent seizure activity without recovery between seizures."

ILAE: Epilepsia 2015. 56(10):1515-1523
Neuro Critical Care Society (2012);
American Epilepsy Society (2016)
Status Epilepticus Guidelines

Most Neurologists and Neuro-intensivists use Guidelines drawn up by:

- American Epilepsy Society
- Neuro-critical Care Society
- National Institute for Health & Care Excellence (NICE)

These guidelines are similar and advise:

- **Stabilisation** of the patient, and then
- **A stepwise approach to the administration of AEDs**
After Stabilisation:
A Staged Approach to AEDs

First-line therapy:
Typically **Benzodiazepine** administration:
*midazolam/lorazepam/diazepam/clonazepam*

Second-line therapy: *(Benzodiazepine-resistant SE)*
Typically **Anti-Seizure Drug** loading:
*phenytoin/fospronatoin/valproate/levetiracetam/phenobarbital*

Third-line Therapy: *(Refractory SE)*
**RSI** and **General anaesthesia**:
*Propofol, midazolam, ketamine*

Forth-line Therapy: *(Super-refractory SE)*
Typically **unproven interventions**
*Hypothermia, vagal nerve stimulation, repetitive transcranial magnetic stim, ketogenic diet, etc.*
Definitions:
Refractory and Super-refractory SE

Refractory SE is defined as continuous seizure activity not controlled by 1\textsuperscript{st} and 2\textsuperscript{nd} line anti-seizure drugs (Benzo’s & AED).

Super-refractory SE is defined as status epilepticus not controlled by third-line agents (i.e. anaesthetic).

Of all patients with status epilepticus:
• 12\% to 43\% progress to refractory SE, and
• 10\% to 15\% progress to super-refractory SE

Guidelines:

1\textsuperscript{st} and 2\textsuperscript{nd} line AEDs are evidence-based

There is now good evidence regarding the choice and dosage of:

- 1\textsuperscript{st} line benzodiazepines
- 2\textsuperscript{nd} line anti seizure drugs (AEDs)

But, evidence guiding 3\textsuperscript{rd} line anaesthetic treatment remains scarce

We will discuss this in more detail later
Despite the progressive introduction of evidence-based SE guidelines, a recent study has shown that there has been no significant improvement in mortality or functional outcomes after SE over the past 30 years.

Why?

• Poor adherence to these guidelines
• 1st and 2nd line drugs are administered too late, and in inadequate dosage
An Overview of Practical Status Epilepticus Management
Is this Status Epilepticus?

1. Is this Status Epilepticus or a seizure which will terminate spontaneously within 5 minutes

2. Is this Status Epilepticus or a mimic?
   - Functional Non-Epileptic Seizure
   - Dissociative seizure
   - Encephalopathy
   - Metabolic derangements
   - etc.

*EEG may be very helpful*
The diagnosis of convulsive status epilepticus is typically straightforward.

**Remember, time is brain**

You need as many hands as you can get because assessment, investigations and management must occur in parallel.

(ideally, 2 doctors and three nurses and any interns who may be standing around)
Convulsive SE Management: Stabilisation Phase

ABC

- Secure airway, decubitus position.
- O₂ Sats monitor, **Face mask O₂** / nasal prongs.
- Send an **urgent blood gas** with electrolytes.
- **Two IV lines** with fluid running.
- Finger prick blood glucose (? Rx Thiamine & glucose).
- **Blood pressure** (hyper/hypotension).
- ECG.
Stabilisation Phase: Focussed Examination

Always keep in mind potentially reversible systemic and intracranial provoking factors

- Fever, rash, signs of head trauma
- Meningism
- Hyper salivation
- Smell (alcohol/liver failure?)
- GCS
- Myosis / midriasis
- Lateralising or localising neurological signs
Stabilisation Phase: 
Focused History

From witness / family member

Keep in mind any reversible provoking factors!

- Known epilepsy?
- Seizure onset and duration
- Comorbidities (diabetes, liver/renal/cardiac)
- Medications
- Psychiatric history (depression, ? para-suicide)
- Recreational drug use (? overdose)
- Recent or distant head injury
- Preceding febrile or other illnesses (meningitis/encephalitis?)
- Prodromal psychiatric / behavioural changes (auto-immune?)
Stabilisation Phase: 
Urgent Lab’s

- Arterial blood gas
- Na K Ca Mg PO
- Acid-base & lactic acid
- FBC, CRP, ESR
- Renal & liver function (ammonia?)
- Toxicology screen
- AED drug level
- Cardiac Markers

(If you suspect bacterial meningitis: blood culture & start IV antibiotics – remember some are epileptogenic)
Convulsive SE Management:  
Stabilisation Phase

Don’t forget chest auscultation and request a mobile chest radiograph

? aspiration pneumonia
Convulsive SE Management:
Stabilisation Phase

Contact ICU

Contact CT scanner

Lumbar puncture after CTB (contrasted if N renal function)

**CSF:** Chemistry
Microscopy
Herpes PCR
IgG index
(TB gene expert)
(auto-immune encephalitis abs)
(syphilis)
(etc.)
Multi-task!

Stabilisation of the patient and early termination of the SE are the first two priorities

Evaluation, stabilisation and management of SE must occur simultaneously.

Early treatment has been shown to be much more effective than late treatment

Use of a **treatment protocol** has been shown to result in better seizure control and shorter admission to ICU and ward

Epilepsia 2010;51(10):2159-2167
First Line Therapy (Adults)
## First Line Therapy: The Evidence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Class, Level of Evidence</th>
<th>Class, Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>Class I, Level A</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Class I, Level A</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Class IIa, Level A</td>
<td></td>
</tr>
<tr>
<td>Phenytoin/fosphenytoin</td>
<td>Class IIb, Level A</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Class IIb, Level A</td>
<td></td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Class IIb, Level A</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class IIb, Level C</td>
<td></td>
</tr>
</tbody>
</table>
First Line Therapy: The Evidence

Veterans Affairs Status Epilepticus Cooperative Study Group Trial (1998)

In terminating Status Epilepticus:

• Benzodiazepines were more effective than phenytoin

• Lorazepam, diazepam or phenobarbital were equally effective

First Line Therapy: The Evidence

**RAMPART study (2012)**

Efficacy pre-hospital administration of IM Lorazepam vs IV Lorazepam for terminating SE

**IM midazolam** (10mg for adults) is as effective as **IV lorazepam** (4mg for adults) in terminating SE.

What about Diazepam?

• A meta-analysis of 5 RCTs showed no statistically significant differences between IV LZP and IV DZP for clinical seizure cessation, ventilator support or clinically relevant hypotension

Epilepsy & Behav 2016;64 29-36

• A comprehensive meta-analysis of 19 studies identified no difference in the efficacy of seizure cessation or adverse effects of non-intravenous MDZ vs. rectal or IV DZP in adults and children

Epilepsy & Behavior, 2015; 49, 325-336
First Line Therapy:
So, Which Benzo?

My personal order of preference is:

- **Lorazepam IV 4mg** (repeat after 5 min x 1 if required)
- **Midazolam IV/IM 10 mg** (typically I do not repeat)
- **Diazepam 10mg IV** (repeat after 5 minutes if required)

Rule of thumb:

- *Use the benzo’ you know and have at hand*
- *But give it early*
- *Use the appropriate dose*

First Line Therapy: The Evidence

Keep in mind:

Up to 70% of patients in SE are under-dosed with a first-line benzo’.

The risk of respiratory depression and hypotension with aggressive benzo’ use is less than that from ongoing convulsive status epilepticus.

Engl J Med 2012;366 591–600
SE Management:

2\textsuperscript{nd} Line Anti-Epileptic Drug (AED)
SE Management:

2nd Line AED

Typically:

All patients with convulsive SE should be loaded with a second-line AED immediately after the first-line benzodiazepine, whether or not status epilepticus has been aborted by benzodiazepines.

SE Management: 2nd Line AED

But which AED is best?

- Phenytoin / Phosphenytoin
- Valproate
- Levetiracetam
- Phenobarbital
Second Line Therapy: The Evidence

2019 ESETT Trial (adults & children)

Levetiracetam, fosphenytoin and sodium valproate are equally effective in the management of benzodiazepine-resistant SE

Termination of SE was only approximately 50% in all arms
- Under-dosing of 1st line benzo’, and
- Delay in initiating 2nd line AED

Levetiracetam and phenytoin were equally effective in inducing SE cessation in children.

Lancet. 2019;393:2125-2134
Second Line Therapy: The Evidence

2019 EcLiPSE Trial (children)

Successive use of phenytoin and levetiracetam was effective in terminating benzodiazepine-resistant SE and associated with extremely low morbidity and mortality.

Lancet. 2019;393:2135-2145
Second Line Therapy: Phenobarbital?

Old drug with significant haemodynamic and respiratory depressive side effects and has fallen out of favour

Has excellent seizure terminating properties, at least equal to those of Phenytoin, valproate and Levetiracetam

Although it is seldom used in adults, there is a large body of evidence of its efficacy in Paediatric literature
Second Line Therapy: Phenobarbital?

Phenobarbital vs. Phenytoin

Single-center randomized parallel clinical trial
144 episodes of SE in 111 children

Termination of benzodiazepine-resistant SE:

- Phenobarbital (20mg/kg): 87% (NNT = 2.5)
- Phenytoin arm (20mg/kg): 46%

Respiratory depression was more common in the Phenytoin!

Burman et al. Frontiers in Neurology 2019 10: article 106
Second Line Therapy: 
Phenytoin

Disadvantages:
• hypotension and cardiotoxicity
• Requires slow administration with cardiac monitoring

Best avoided in:
• TCA / cocaine overdose and toxidromes
• Liver failure
• Cardiac history
• Already therapeutic on Phenytoin
  • Unlikely to be effective
  • Risk of cardiac toxicity
Second Line Therapy: Phosphenytoin

Phosphenytoin vs Phenytoin

- Water soluble
- Fewer cardiovascular side effects
  (Does not contain propenyl gluconate)
- Fewer drip-site reactions
- May be infused more quickly
Second Line Therapy: Valproate

- May be infused more rapidly than phenytoin/phosphenytoin
- Better side effect profile
- Avoid in women of child bearing potential

*Always exclude eclampsia as a cause for SE in women, which is best treated with magnesium sulphate!*
Second Line Therapy: Levetiracetam

ESETT, ConSEPT and EcLiPSE have all demonstrated that levetiracetam is a viable alternative to phenytoin.

Advantages:

- Speed of administration
- Absence of adverse cardiovascular effects
- Low drug-drug interactions
- Simpler pharmacokinetics

In future, levetiracetam will probably supersede phenytoin as the default treatment in benzodiazepine-resistant SE.

BRAIN 2021: 144; 1336–1341
Second Line Therapy: Which AED at What Dose?

In short, all of the following agents are acceptable as 2\textsuperscript{nd}-line AED in convulsive SE:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam</td>
<td>40-60mg/kg</td>
</tr>
<tr>
<td>Valproate</td>
<td>20-40mg/kg</td>
</tr>
<tr>
<td>Phenytoin / Phosphenytoin</td>
<td>20mg/kg</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>15-20mg/kg</td>
</tr>
</tbody>
</table>

Load early and do not under-dose!
Second Line Therapy: Which AED?

The choice of 2\textsuperscript{nd}-line AED depends on:

- Availability
- Familiarity with the drug
- Patient-related factors
- Side effect profile
Third Line Therapy:
Super-refractory SE: **Intubation & Anaesthesia**

https://www.irvinedentalcare.com/blog/intubation
Third Line Therapy:
Rapid Sequence Intubation (RSI) & Anaesthesia

When to intubate?

• Ongoing clinical or electrographic seizure activity after 1\textsuperscript{st} and 2\textsuperscript{nd} line AED loading

• Intubate earlier if:
  • Respiratory depression
  • Haemodynamic instability
  • Very ill patients
Third Line Therapy: Intubation & Anaesthesia

Remember:

Risk of respiratory depression, cardiovascular collapse and brain injury is increased in patients with ongoing seizures

Some even suggest going straight to intubation and anaesthesia before loading with second-line AEDs
But this is a minority opinion
Also keep in mind:

Just because a patient is not clinically convulsing after 1\textsuperscript{st} and 2\textsuperscript{nd} line treatment, this does not exclude ongoing subclinical ("subtle") status epilepticus
Identifying Non-Convulsive / “Subtle Status Epilepticus

Suspect if the patent remains persistently unresponsive despite no overt clinical signs of seizure activity

Clinical

• Gaze deviation,
• nystagmus,
• subtle conic movements face/fingers,
• lip smacking,
• subtle hippus of a pupil

EEG is extremely helpful if available
EEG:
Subclinical Electrographic SE
Routine vs. Continuous EEG for Subclinical SE

• A 30 minute **routine EEG** will identify approximately 25% of sub-clinical SE

• 24 hours of **continuous video-EEG** monitoring will identify 90% of subclinical SE
It is important to know a little about the paralytic and anaesthetic agents which the anaesthetist / intensivist may administer to your patient.
RSI:
Paralysing Agents for Intubation

- **Succinylcholine** (depolarising)
  - Disadvantages:
    - **Hyperkalaemia** after prolonged seizures (rhabdomyolysis)
    - Avoid in renal failure, neuromuscular disorders
  - Advantages:
    - Rapid onset & **short duration** (10 min)

- **Rocuronium** (non-depolarising)
  - Disadvantages:
    - slow onset & **long duration** (60-90 min)
    - Clinical assessment not possible
    - Requires EEG confirmation of seizure control
  - Advantages:
    - Reversible using sugammadex (expensive)
Third Line Therapy (Super-Refractory SE): Anaesthesia

Which Anaesthetic Agent?

- Midazolam
- Propofol
- Pentobarbital
- Ketamine

All have pro’s and cons

No good evidence for which is best

*Midazolam and Propofol are the most widely used*
Which Anaesthetic Agent: Induction & Post-Induction Sedation

- **Midazolam**
  - Safe and less vasoactive than Propofol
- **Propofol**
  - Hypotension in high doses
  - More likely to require vasopressor support
- **Ketamine** (Little evidence)
  - Seems to be good agent in hypotensive patients
  - ? Neuroprotective anti-NMDA activity?
- **Etomodate** (used for induction)
  - Associated with myoclonic jerks in up to 30%
  - ? Reduced seizure threshold
Third Line Therapy:
Anaesthesia

Bear in mind:

• **Almost all seizures should be suppressible on adequate doses of anaesthetic agents**

• **Anaesthetic doses required for the management of status epilepticus are typically much higher than those used for sedation in most other conditions**
Anaesthesia:
EEG Confirmation of Seizure Suppression

After anaesthesia has been initiated, and there is no longer clinical evidence of seizure activity, another EEG should be performed to confirm either:

• Cessation of electrographic seizure activity

• A burst-suppression pattern
EEG Confirmation of Seizure Suppression: Burst-Suppression Pattern
General anaesthesia is typically continued for 24 - 48 hours before weaning.

*There little good evidence for this*
Anaesthesia:  
After Weaning

After weaning:

If clinical and/or electrographic seizure activity persists, the patient is typically re-anaesthetised for another 24 – 48 hours

However, there is debate about what to do in the case of many abnormal EEG patterns which fall in the ictal-interictal continuum...

Does one continue to wean or re-anaesthetise?
Ictal-Interictal Continuum: Lateralised Periodic Discharges
Ictal-Interictal Continuum: Generalised Periodic Discharges
Ictal-Interictal Continuum: Lateralised Delta Slowing
Status Epilepticus
The Role of Brain imaging
Once seizures are controlled, virtually all stabilised patients will require brain imaging to exclude structural or inflammatory intracranial pathology.

Contrasted CTB Scan (if normal renal function)
Brain Imaging

CT

Meningitis
Traumatic Brain Injury
Intracerebral Haemorrhage
Metastasis
Glioma
Neurocisticercosis

Source: Radiopedia
Brain Imaging
CT

Keep in mind that changes related to prolonged SE may be seen on CT, and mistaken for other pathology:

These include

• Oedema
• Loss of grey–white matter differentiation
• Sulcal effacement
• Gyriform enhancement
If CT is “normal”, MRI may be performed to exclude more subtle structural intracranial abnormalities.
Status Epilepticus-related hippocampal changes (Flair sequence)

http://www.radiologyassistant.nl
Brain Imaging: MRI

In prolonged SE, restricted diffusion sequences may closely resemble an ischaemic infarction.

These changes are typically seen in the cortex and hippocampi.

But other structures can also be affected:
- basal ganglia
- corpus callosum
- thalami

*Neurology* 1999; 52: 1021–27; *Epilepsy Behav* 2014; 33: 24–30
SE-related changes resembling cerebral infarction

MRI

Diffusion weighted imaging (A) and restricted diffusion (B)

Lancet Neurol 2015:14:615-24
Convulsive Status Epilepticus: In Short...

- Convulsive status is a **neurological and medical emergency**
- Your first priorities are **stabilisation** of the patient and early **termination of the status**.
- As well as the identification of any underlying **provoking factors**
Convulsive Status Epilepticus: In Short...

- Therapeutic delay and under-treatment are recognised as significant factors influencing both morbidity & mortality.

- There is good evidence regarding the choice and dosage of: 1st line benzodiazepines, and 2nd line AEDs but little evidence guiding 3rd line anaesthetic management.

- Use a recognized treatment protocol.
Thank you