Status epilepticus – an update on treatment

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Definitions

• Over 30 years ago the ILAE defined Status Epilepticus as a convulsive seizure lasting > 30 minutes or a failure to recover function following a series of convulsive seizures over 30 minutes.

• In 1999 an Operational Definition was introduced that defined status epilepticus as $\geq 5$ min of (1) continuous seizure or (2) two or more discrete seizures between which there is incomplete recovery of consciousness.
Key time periods in natural history of seizure

- Interval within which most seizures spontaneously stop
- Optimum interval for initiation of rescue therapy
- Time definition for CSE for treatment purposes (operational definition)
- Time definition for CSE for epidemiological, pathophysiological and outcome purposes

Time after onset of seizure (minutes)
Conceptual definition

“SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point $t_1$). It is a condition that can have long-term consequences (after time point $t_2$), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.”
<table>
<thead>
<tr>
<th>Type of SE</th>
<th>Time (t1), when a seizure is likely to be prolonged leading to continuous seizure activity</th>
<th>Time (t2), beyond which long term consequences are increasingly likely (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic clonic SE</td>
<td>5 minutes</td>
<td>&lt;30 minutes</td>
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<tr>
<td>SE with dyscognitive symptoms</td>
<td>5 minutes*</td>
<td>30-60 minutes*</td>
</tr>
<tr>
<td>Absence status epilepticus</td>
<td>2 minutes**</td>
<td>unknown*</td>
</tr>
</tbody>
</table>

**Implications to treatment**

- **Time point 1** determines the earliest time when treatment should be considered or started
- **Time point 2** determines the time at which status should be controlled to prevent long term consequences

* Best available evidence, but insufficient data to give a definite timepoint
Who is at risk of status epilepticus?

• Between four and eight children per 1000 are expected to experience CSE before age 15 years.
• It is the most common medical neurological emergency in children.
• In >50% of children presenting with status epilepticus it will be their **first** seizure.
• A history of status epilepticus is the most common risk factor for recurrent status epilepticus.
• Other common risk factors for pediatric SE include a younger age (<2 years), a symptomatic etiology (structural/metabolic); and a history of an epileptic encephalopathy or a specific epilepsy syndrome (e.g. Dravet Syndrome).
Who is at risk of status epilepticus?

- Seizures of partial onset had an increased tendency to be prolonged, compared to generalised seizures.
- A population-based study from Finland in which 150 children with new-onset epilepsy were followed for more than 30 years (febrile status was excluded), found that 27% of these patients suffered at least one SE. Of these children, 90% presented with a status within the first two years following diagnosis.
FEBSTAT Study

• FEBSTAT is a prospective multicenter study investigating the consequences of febrile status epilepticus in childhood.

• Early results showed the median age was 1.3 years, the mean peak temperature was 39.5°C, and seizures lasted a median of 68.0 minutes.

• Seizures were continuous in 52% and behaviorally intermittent (without recovery in between) in 48%; most were partial (67%) and almost all (99%) were convulsive.

• In one third of cases, FSE was unrecognized in the emergency department.
Febrile status often requires more than one drug to terminate, although this may reflect delayed administration.

The median time from seizure onset to the first drug by the emergency medical services or the emergency department was 30 minutes.

The mean seizure duration was 81 minutes for patients given medication prior to the emergency department and 95 minutes for those who did not.

Reducing the time from seizure onset to anti-epileptic drug initiation was significantly related to shorter seizure duration.
Other findings of the FEBSTAT study.

- 22/226 imaged with MRI post FSE had hippocampal T2 hyperintensity. Of these 14 had follow up MRIs, 10 showed Hippocampal sclerosis on expert review, and 12 had reduced hippocampal volume on volumetric assessment.
- HHV-6B was found in 54/169 patients tested accounting for 32%, and HHV-7 detected in 12 (7.1%).
- Hippocampal malrotation was found in 20/226 patients with FSE (predominantly found on the left only, and more commonly in boys). This is suggestive that malrotation is a cortical malformation rather than a normal variant.
Table 5  Status epilepticus due to genetic diseases (103) (see Supplementary Table 2 for additional references).

<table>
<thead>
<tr>
<th>Chromosomal aberrations</th>
<th>Malformations of cortical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ring chromosome 20</td>
<td>1. Focal cortical dysplasias</td>
</tr>
<tr>
<td>2. Angelman syndrome</td>
<td>2. Hemimegalencephaly</td>
</tr>
<tr>
<td>5. XLMR syndrome</td>
<td>5. Schizencephaly</td>
</tr>
<tr>
<td>6. Ring chromosome 17</td>
<td>Neurocutaneous syndromes</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>1. Sturge Weber syndrome</td>
</tr>
<tr>
<td>1. Porphyria</td>
<td>2. Tuberous sclerosis</td>
</tr>
<tr>
<td>2. Menkes disease</td>
<td>Others</td>
</tr>
<tr>
<td>3. Wilson’s disease</td>
<td>1. Dravet syndrome</td>
</tr>
<tr>
<td>4. Adrenoleukodystrophy</td>
<td>2. Familial hemiplegic migraine</td>
</tr>
<tr>
<td>5. Alexander disease</td>
<td>3. Progressive myoclonus epilepsies</td>
</tr>
<tr>
<td>7. OTC deficiency</td>
<td>5. Wrinkly skin syndrome</td>
</tr>
<tr>
<td>10. 3-Methylcrotonyl CoA carboxylase deficiency</td>
<td>8. Wolfram syndrome</td>
</tr>
<tr>
<td>11. Lysinuric protein intolerance</td>
<td>9. AR hyperekplexia</td>
</tr>
<tr>
<td>13. Metachromatic leukodystrophy</td>
<td>11. CADASIL</td>
</tr>
<tr>
<td>15. Beta ureidopropionase deficiency</td>
<td>13. LYK-5 mutation</td>
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<tr>
<td>16. 3 hydroxyaxyl CoA dehydrogenase deficiency</td>
<td>14. MECP2 mutation</td>
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<tr>
<td>17. Carnitine palmytoytransferase deficiency</td>
<td>15. Malignant hyperpyrexia</td>
</tr>
<tr>
<td>18. Succinic semialdehyde dehydrogenase deficiency</td>
<td></td>
</tr>
</tbody>
</table>

Selected references (principal references in bold): Chromosomal aberrations: 1. (Biraben et al., 2004; Inoue et al., 1997), 2. (Ohtsuka et al., 2005; Sugimoto et al., 1992), 3. (Battaglia et al., 1999); Inborn errors of metabolism: 1. (Bhatia et al., 2008; Zaatreh, 2005), 2. (Bahi-Buisson et al., 2006), 3. (Turk-Boru et al., 2003); Malformations of cortical development: 1. (Fauser et al., 2006); Others: 1. (Buoni et al., 2006), 2. (Beauvais et al., 2004), 3. (Kumada et al., 2006).
Diagnosis

• The diagnosis of convulsive status epilepticus (tonic-clonic movements) is usually straightforward – however, failure to recover between seizure episodes can make assessment difficult. Close observation of the ‘post-ictal’ patient is important – specifically for intermittent jerking or tonic stiffening.

• Differential: - non-epileptic events (which are most common in patients with epilepsy)
  - acute dyskinesias in patients with known cerebral palsy.

• Unless the history of non epileptic events is known, it is generally preferable to treat.
Pre-hospital management.

- Benzodiazepines are recommended as the initial drug of choice for treating SE.
- Midazolam Buccal/Nasal (0.3mg/kg)/IMI/IV(0.15mg/kg).
- There has been ongoing argument about Lorazepam vs Midazolam vs Diazepam with various methods of administration Buccal/Nasal/IM/IV.
- Lorazepam is not widely available and IM Midazolam has been part of the protocol of NSW Ambulance since 2006.
• IM Midazolam compared favourably with IV Lorazepam for seizure termination, hospital and ICU admission, ET intubation and seizure recurrence. The speed and ease of administration supported its use by paramedics as a first line agent.
Prospective observational cohort study.

81 patients (44 male) with a median age of 3.6 years. (47% with known epilepsy, and 17% with previous SE)

The first, second, and third AED doses were administered at a median time of 28 minutes, 40 minutes, and 59 minutes after SE onset.

The first and second doses of non-benzodiazepine AEDs were administered at 69 minutes and 120 minutes.

In the 64 patients with out-of-hospital SE onset, 40 (62.5%) patients did not receive any AED before hospital arrival.

In the hospital setting, the first and second in-hospital AED doses were given at 8 (5–15) minutes and 16 (10–40) minutes after SE onset
Risks of excessive Benzodiazepines.

• Maximum of 2 doses at least 5 minutes apart before using a second agent.
• A recent study from SCH, Randwick – showed that while it useful to have Guidelines – they should generally be followed!
• A review of 21 patients retrieved by NETS (all intubated) for SE, showed that 85% (18) had deviated from protocol, 17 of these had been excessive dosing with benzodiazepines with one patient receiving 13 doses...
• This echoes a previous study from Chin et al (2004) which showed that most children admitted to Intensive care were less than 5, had their first episode of status and had received more than 2 dose of benzodiazepines.
• Do not disregard pre-hospital treatment!
### Table 3. Recommendations for diagnostic evaluation of child presenting in status epilepticus

<table>
<thead>
<tr>
<th>New-onset status epilepticus</th>
<th>Status in known epilepsy patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Always recommended:</strong></td>
<td><strong>Always recommended:</strong></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>AED levels</td>
</tr>
<tr>
<td>EEG</td>
<td></td>
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<tr>
<td>CT/MRI</td>
<td></td>
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<tr>
<td><strong>If clinical suspicion:</strong></td>
<td><strong>Consider:</strong></td>
</tr>
<tr>
<td>Urine toxicology</td>
<td>Electrolytes</td>
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<tr>
<td>Genetic/metabolic testing</td>
<td>EEG</td>
</tr>
<tr>
<td>Lumbar puncture&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Genetic testing</td>
</tr>
<tr>
<td></td>
<td>CT/MRI</td>
</tr>
<tr>
<td><strong>Add if febrile:</strong></td>
<td><strong>Consider if febrile:</strong></td>
</tr>
<tr>
<td>CBC</td>
<td>CBC</td>
</tr>
<tr>
<td>Lumbar puncture&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lumbar puncture</td>
</tr>
<tr>
<td><strong>If refractory or persistent encephalopathy:</strong></td>
<td><strong>If refractory or persistent encephalopathy:</strong></td>
</tr>
<tr>
<td>Continuous video EEG</td>
<td>Continuous video EEG</td>
</tr>
</tbody>
</table>

<sup>a</sup> Lumbar puncture is not recommended in children with possible infection or mass lesion.
2\textsuperscript{nd} line/Urgent treatment.

- Approximately one third of SE patients continue to have seizures despite administration of adequate doses of benzodiazepines.
- There are no Class 1 clinical trials comparing the efficacy of currently available medications for the treatment of ‘Established’ S.E.
- Phenytoin vs Phenobarbitone vs Levetiracetam vs Valproate.
2nd line/Urgent treatment.

- The majority of guidelines worldwide (NICE, Canadian Pediatric Society, NSW Health Department, Boston Children’s Hospital) would recommend Phenytoin/Fosphenytoin as the 1st choice agent.
- These choices are essentially based on the fact that these drugs have been available for much longer than any new AED. They are time-tested and there is abundant literature on their efficacy.
- Levetiracetam has some attractive features (although it is more the potential sfx of phenytoin that bolster Levetiracetam) in that it has few drug interactions, there is no extravasation risk, it is not metabolized and can be delivered relatively quickly and does not cause hypotension or arrhythmia.
- Studies in children have involved small numbers and the safety profile appears good.
2\textsuperscript{nd} line/Urgent treatment.

- A retrospective study comparing phenytoin, valproate and levetiracetam in 167 adults and a systematic evaluation of published evidence (predominantly case series, and only one randomised double blinded trial) suggest that levetiracetam and valproate have similar efficacy to phenytoin/fosphenytoin and phenobarbital.

- Potentially best results were obtained for Valproate
Highlighting the different sites of action of various anticonvulsants. The basis for ‘Rational polypharmacy’ – using multiple agents with different mechanisms.

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**Figure** | **Mechanism** | **Anticonvulsant**
--- | --- | ---
1 | VG-Na⁺ Channel | Carbamazepine, Eslicarbazepine acetate, Felbamate, Lamotrigine, Oxcarbazepine, Phenytoin, Pregabalin, Topiramate, Valproate, Zonisamide
2a | VG-Ca⁺ Channel (L-type) | Gabapentin, Pregabalin
2b | VG-Ca⁺ Channel (T-type) | Ethosuximide, Topiramate, Valproate, Zonisamide
2c | VG-Ca⁺ Channel (N + P type) | Lamotrigine
3 | GABA₅ receptor (agonist) | Barbituates, Benzodiazepines, Felbamate, Topiramate
4 | GABA, | Propofol
5 | GABA uptake inhibitor | Tiagabine
6 | GABA-transaminase inhibitor | Vigabatrine
7 | GAD modulation | Gabapentin, Valproate
8 | SV2A | Levetiracetam
9a | AMPA, kainate receptor | Phenobarbital, Topiramate
9b | AMPA, non-competitive antagonist | Perampanel
10 | NMDA receptor | Felbamate, Ketamine, Propofol, Magnesium
The Established SE Treatment Trial (ESETT), a large international collaboration, is a randomized controlled, double-blinded trial to definitively establish whether valproate and/or levetiracetam are superior to (fos)phenytoin as second-line treatment for SE.
**ASSESSMENT AND INITIAL MANAGEMENT**

**Time from onset of seizure (in minutes)**

- **5 minutes**
  - Vascular access obtained (within 1 minute)
    - Midazolam or Diazepam given < 1 hr prior to presentation should be regarded as 'initial doses already given' within this flowchart.
    - If BGL < 3.5
      - Give 5 mL/kg 10% Dextrose IV (as bolus)
      - Then commence 5 mL/kg per hour 10% Dextrose IV infusion and REPEAT BGL within 5 mins
    - Either:
      - Midazolam 0.15 mg/kg IV (max 5 mg)
      - Diazepam 0.25 mg/kg IV (max 10 mg)

- **10 minutes** still fitting
  - Repeat either:
    - Midazolam 0.15 mg/kg IV OR
    - Diazepam 0.25 mg/kg IV

- **5 minutes** still fitting
  - Vascular access obtained
  - Attempt intravenous access
    - Collect blood (as below)
    - Check blood glucose
  - Either:
    - Midazolam 0.3 mg/kg Buccal or Intranasal (max 10 mg) OR
    - Midazolam 0.15 mg/kg IM (max 5 mg) OR
    - Diazepam 0.5 mg/kg PR (max 10 mg)

- **5 minutes** still fitting
  - Repeat either:
    - Midazolam 0.3 mg/kg Buccal OR
    - Midazolam 0.15 mg/kg IM OR
    - Diazepam 0.5 mg/kg PR

**Establish airway — Oxygen**
- Seek senior advice and assistance if necessary.
Seizure Terminated

- Position child in Recovery position, on left side. Maintain airway (jaw thrust, chin lift, suction).
- History/examination: Search for underlying cause (head injury, sepsis, meningitis, metabolic). And include localisation of infection when febrile (when appropriate refer to other Clinical Practice Guidelines e.g. Fever, Meningitis, Recognition of the Sick Child). A drug history should be taken and signs of unexpected autonomic disturbance sought in the examination, including unexpected pupillary signs, pulse rate or blood pressure. If toxicity is established, contact the Poisons Information Centre on 131126 for advice on specific treatment.
- Blood Glucose should be measured in any child who is continuing to fit, or has not regained full consciousness at presentation. EUC should be collected if there has been repeated diarrhoea or vomiting. Anticonvulsant levels should be measured if previously regularly administered. Calcium should be measured on first presentation of fits without fever. Blood count and culture should be collected if a child has prolonged seizure with fever, or if sepsis is suspected. Cerebral imaging should be arranged if seizure has been focal. Lumbar Puncture should be arranged if meningitis is suspected and there are no contra-indications (See Meningitis Management Guidelines.)
- Consider antibiotics if bacterial sepsis cannot be excluded.
Seizure Terminated

- Position child in Recovery position, on left side. Maintain airway (jaw thrust, chin lift, suction).
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- Consider antibiotics if bacterial sepsis cannot be excluded.
Paraldehyde

- Not a bad anticonvulsant in status – but now largely superseded by benzodiazepines.
- Can be given rectally or IM.
- Studies as recent as 2009 show it was effective terminating status epilepticus in 62% of children, and 76% of children with status epilepticus and known epilepsy.
- Difficult to acquire now and very expensive >$500/vial.
- Said to be carcinogenic....... Like bacon, salami and vegetable oil...
- It has now largely fallen off most protocols – but importantly the risk of respiratory depression is low and there may be a role for children in remote locations at risk of status if it can be obtained.
Seizure → Ambulance → Emergency Department → Intensive Care Unit
Seizure
Ambulance
Emergency Department
Intensive Care Unit
Paediatrician contacted
Paediatric Neurologist contacted
Where can the Paediatrician get involved?

- Individual Seizure Management plan for those at risk of Status, e.g. SCN1A “BE PREPARED”
- Awareness of local hospital seizure protocol/clinical guideline
Individual seizure management plan.

- Recommended for all children known to have convulsive seizures lasting longer than 5 minutes and partial seizures longer than 5-10 minutes.
- Recommendations should reflect the individual’s seizure pattern.
- Special consideration to patients in remote locations and those travelling.
- Seizure management plans are often written for outside agencies (childcare/preschool/school) where there may be reluctance to deliver medication because of concerns about legal liability if something goes wrong and perhaps a concern regarding lack of formal training.
- Epilepsy Action can provide specific training to schools both within suburban and rural regions.
- Short courses of longer acting benzodiazepines such as Clobazam can be considered in patients with known risk factors – such as fever and SCN1A, or other syndromes with susceptibility to status with recognised provoking factors prior to seizure onset.
SEIZURE MANAGEMENT PLAN for Parents/Carers

M__ T_______      DOB: 15/03/2013      CHW 1186325

In the event of a tonic clonic seizure (loss of awareness, body stiffening followed by jerking of one or more limbs):

1. Stay calm
2. Time the event
3. Place Max in a side lying position (recovery position) to keep his airway clear
4. Provide comfort, reassurance and a safe environment
5. Check his breathing and stay with Max during the event

6. If the seizure is still going at 3 minutes administer midazolam 5mg (1 vial x 5mg/ml) into the nasal cavity or inside the cheek.

7. If the seizure is still going 5 minutes after giving midazolam call an ambulance dial 000

8. If the seizure stops, allow Max to sleep or rest.
Seizure

Ambulance

Emergency Department

Intensive Care Unit

8-15 min

30 min

1 hour plus

Paediatrician notified

Neurology notified
Refractory Status

• The Neurocritical Care Society (US) guideline states that “patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable anticonvulsant will be considered refractory.”

• Many protocols suggest infusions at this point, however – alternative second line agents (levetiracetam/valproate/phenobarbitone) have a role here, and may help avoid the need for intubation which often follows with benzodiazepine infusions, and almost invariably with thiopentone infusions.

• Continuous EEG monitoring is recommended at this point.
The Role of EEG.

• The Neurocritical Care Society has recommended Continuous EEG monitoring is usually required for the monitoring of SE. It should be initiated within one hour of SE onset, and should continue for 48 hours to evaluate for non-convulsive status.

• The availability to do this even in tertiary centres in Australia is often limited.
Continuous EEG monitoring

• The goal of CEEG is to maximize the early detection and treatment of seizures and, ultimately, to minimize secondary neuronal and systemic injuries that can arise from ictal activity.

• Studies suggest that seizures—including Non-convulsive Seizures—in the acutely injured brain can cause a variety of adverse physiological effects, such as increases in cerebral blood flow, intracranial pressure, metabolic demand and mass effect; acute elevations in lactate, glutamate and neuron-specific enolase levels; and delayed hippocampal atrophy and chronic epilepsy.

• Additionally, nonconvulsive seizures, especially when prolonged, have been independently associated with poor outcomes, including functional ability and quality of life.
Super Refractory Status

- Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24h or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia.
General anaesthesia (including consideration of ketamine), antiepileptic drugs and full ITU support; and investigate urgently to identify cause.

- No cause identified
  - Give IV magnesium (& IV pyridoxine in children)
    - Consider steroids +/- IVIg +/- PEX
    - Consider hypothermia
    - Consider ketogenic diet
    - Consider ECT, CSF drainage and other therapies, see text
  - Consider neurosurgery in lesional SE
- Cause identified
  - Treat cause if possible

Neuroactive steroids for the treatment of status epilepticus

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Summary

Benzodiazepines are the current first-line standard-of-care treatment for status epilepticus but fail to terminate seizures in about one third of cases. Synaptic GABA_A receptors, which mediate phasic inhibition in central circuits, are the molecular target of benzodiazepines. As status epilepticus progresses, these receptors are internalized and become functionally inactivated, conferring benzodiazepine resistance, which is believed to be a major cause of treatment failure. GABA_A receptor positive allosteric modulator neuroactive steroids, such as allopregnanolone, also potentiate synaptic GABA_A receptors, but in addition they enhance extrasynaptic GABA_A receptors that mediate tonic inhibition. Extrasynaptic GABA_A receptors are not internalized, and desensitization of these receptors does not occur during continuous seizures in status epilepticus models. Here we review the broad-spectrum antiseizure activity of allopregnanolone in animal seizure models and the evidence for its activity in models of status epilepticus. We also demonstrate that allopregnanolone inhibits ongoing behavioral and electrographic seizures in a model of status epilepticus, even when there is benzodiazepine resistance. Parenteral allopregnanolone may provide an improved treatment for refractory status epilepticus.

Key Words: Refractory status epilepticus, Seizure, Allopregnanolone, Neurosteroid, Allosteric modulator, Extrasynaptic GABA_A receptor.

Pediatric Super-Refractory Status Epilepticus Treated with Allopregnanolone

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Super-refractory status epilepticus is a life-threatening condition. Resistance to benzodiazepine and barbiturate treatment for this disorder is thought to be due to internalization of synaptic γ-aminobutyric acid (GABA)₁ receptors, and withdrawal of benzodiazepines and barbiturates during treatment often triggers seizure recurrence. The neurosteroid allopregnanolone acts as a positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors. Here we describe the use of allopregnanolone in 2 pediatric patients with super-refractory status epilepticus. This treatment allowed the general anesthetic infusions to be weaned with resolution of status epilepticus. This is the first report of allopregnanolone use to treat status epilepticus in children.

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Outcome

- Morbidity and mortality are largely related to status epilepticus cause, but duration is also important and is the only modifiable variable.
- Children with febrile status epilepticus or epilepsy-related status epilepticus have a 0–2% mortality whereas children with acute symptomatic status epilepticus have a 12 – 16% mortality.
- Of children without prior epilepsy, 30% had subsequent seizures
Status Epilepticus: Think Time

- **Time** to treatment needs to be shorter.
- Response to treatment is **time** dependent.
- Morbidity and mortality are related to etiology and **duration (time)** of status epilepticus.
- Subsequent epilepsy may depend on the **duration (length of time)** of the status epilepticus.
- **Prolonged** seizures predict future **prolonged** seizures.
Seizure onset $T^0$

5 Min

- ‘Impending CSE’
  - 2 doses of Benzodiazepine, 5 minutes apart

15 minutes

- ‘Established CSE’
  - IV Phenytoin 20mg/kg, will take 20 min at least
  - If still seizing
    - IV Levetiracetam 30mg/kg or
    - IV Valproate 30mg/kg

35 minutes

- ‘Refractory CSE’
  - Midazolam Infusion/Thiopentone infusion for Pharmacologic Coma
  - Establish EEG monitoring.

1 hour

- ‘Super Refractory CSE
  - Consider Ketamine infusion

24 hours
Important points

• Benzodiazepines at **5 minutes**.

• Active management plans for patients with previous status and those at risk of status. (Young patients, structural brain abnormalities, genetic and metabolic conditions)

• Not more than 2 doses of benzodiazepine.

• 2\textsuperscript{nd} line agents can almost invariably be started the moment a child arrives in ED with a cannula.