**STATUS EPILEPTICUS**
*A Practical Approach to Treatment*

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**Definition**

Conventional definition:
- Single seizure > 30 minutes
- Series of seizures > 30 minutes without full recovery

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**Definition**

Official definition:
Continuous seizure activity lasting >10 minutes
or
Two or more discrete seizures with incomplete recovery of consciousness between them

~150,000 cases annually in the United States

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**Continuum of seizures to SE**

- Isolated Seizures
- Prodromal Stage
- Incipient SE
- Early SE
- Established SE
- Refractory SE
- Malignant SE

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**Status Epilepticus (SE)**

- “If appropriate therapy is delayed, SE can cause permanent neurologic sequelae or death …”

thus

“… any child who presents actively convulsing should be assumed to have SE.”


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**The longer SE persists,**

- The lower is the likelihood of spontaneous cessation
- The harder is it to control
- The higher is the risk of morbidity and mortality

- Treatment for most seizures needs to be instituted after > 5 minutes of seizure activity

Bleck TP. Epilepsy 1999;40(1):S64-6
Prolonged seizures

Duration of seizure

Temporary systemic changes

Life threatening systemic changes

Death

Pathophysiology

GABA<sub>A</sub> receptor internalization and/or subunit rearrangement such that they lose diazepam sensitivity

Status Epilepticus-induced Injury

Dentate granule cells and hilar interneurons are damaged after pilocarpine-induced seizures in rats pretreated with lithium. Injured cells appear bright.


Status Epilepticus (SE)

SE presents in a multitude of forms, depends on etiology and patient age (myoclonic, tonic, tonic-clonic, absence, complex partial etc.)

Types of SE

Convulsive SE
- Generalized convulsive (GCSE) is the most common and the most dangerous form of SE
- Focal convulsive (FCSE)
- If untreated, may progress to nonconvulsive SE

Nonconvulsive SE
- Absence — considered benign
- Focal NCSE — not benign; get cycling between levels of responsiveness and unresponsiveness
- NCSE in coma

Type of SE: seminology

CSE

NCSE

Generalized CSE
- Tonic
- Clonic
- Tonic-clonic

Absence SE
- Typical

Focal CSE
- Focal motor
- with 2° GTCS

Focal NCSE
- Sensory symptom
- Affective symptom
- Complex partial SE

SE in coma
Etiology of SE: etiology

<table>
<thead>
<tr>
<th>Type of SE</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Acute symptomatic</td>
<td>SE occurring during an acute illness (an acute CNS insult) or an acute encephalopathy</td>
<td>Meningitis, encephalitis, electrolyte disturbances, sepsis, hypoxia, trauma, intoxication</td>
</tr>
<tr>
<td>2) Remote symptomatic</td>
<td>SE occurring without an acute provocation to a patient with a prior history of a CNS insult (a chronic encephalopathy)</td>
<td>CNS inflammation, previous traumatic brain injury, chromosomal disorder</td>
</tr>
<tr>
<td>3) Remote symptomatic with an acute precipitant</td>
<td>SE occurring with a chronic encephalopathy, but with an acute provocation</td>
<td>CNS inflammation or previous CNS insult with concomitant disease; hypoglycemia, hypocalcemia, intoxication</td>
</tr>
<tr>
<td>4) Progressive encephalopathy</td>
<td>SE occurring with an underlying, progressive CNS disorder</td>
<td>Mitochondrial disorders, CNS lipid storage diseases, amino acidopathies, organic acidopathies</td>
</tr>
<tr>
<td>5) Febrile</td>
<td>SE occurring when the only provocation is a febrile illness, after excluding a direct CNS infection</td>
<td>URI, sinusitis, sepsis</td>
</tr>
<tr>
<td>6) Idiopathic</td>
<td>SE occurring in the absence of an acute provoking CNS insult, systemic metabolic disturbance, or both</td>
<td>No definable cause</td>
</tr>
</tbody>
</table>

![Etiology of SE in Adults and Children](chart1)

<table>
<thead>
<tr>
<th>Etiology of SE (in children)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td>Fever or systemic infection</td>
</tr>
<tr>
<td>Discontinuation / change of AEDs</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Metabolism</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Atonia</td>
</tr>
<tr>
<td>CNS infection</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td>Alcohol withdrawal</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
</tbody>
</table>

*Adapted from Towne AR et al. Epilepsia. 1994;35:27-34.
**Adapted from DeLorenzo RJ et al. Epilepsia. 1992;33(suppl4):15-25

![Mortality (in adults)](chart2)

Mortality (in adults)

- 10-20%, highest with stroke, hypoxia, CNS infection
- Mortality
  - Adults: 15 – 22%
  - Children: 3 – 15%

EEG patterns of CSE

<table>
<thead>
<tr>
<th>EEG Findings</th>
<th>Percent</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>3.3</td>
<td>0-34</td>
</tr>
<tr>
<td>Generalized slowing</td>
<td>41.0</td>
<td>26-93</td>
</tr>
<tr>
<td>Focal slowing</td>
<td>6.3</td>
<td>0-23</td>
</tr>
<tr>
<td>Epileptiform features, generalized only</td>
<td>8.6</td>
<td>0-19</td>
</tr>
<tr>
<td>Epileptiform features, focal only</td>
<td>16.0</td>
<td>0-47</td>
</tr>
<tr>
<td>Epileptiform features, generalized and focal</td>
<td>19.1</td>
<td>0-42</td>
</tr>
<tr>
<td>Electroencephalographic inactivity</td>
<td>1.8</td>
<td>0-3.9</td>
</tr>
</tbody>
</table>

EEG stages of CSE

- **Stage 1**: Discreet seizures with interictal slowing
- **Stage 2**: Merging seizures with waxing and waning of ictal discharges
- **Stage 3**: Continuous ictal discharges
- **Stage 4**: Continuous ictal discharges punctuated by flat periods
- **Stage 5**: Periodic epileptiform discharges (PEDS)

EEG stage 1: Discreet seizures with interictal slowing

EEG stage 2: Waxing and waning of ictal discharges

EEG stage 3: Continuous ictal discharges
**EEG stage 4:**
Continuous ictal discharges with suppression background

**EEG stage 5:**
Periodic epileptiform discharges

**Nonconvulsive status epilepticus (NCSE)**

- How do you tell that patient’s seizures have stopped?

**Nonconvulsive SE ?**

- Neurologic signs after termination of SE are common:
  - Pupillary changes
  - Abnormal tone
  - Babinski
  - Posturing
  - Clonus
  - May be asymmetrical

**Nonconvulsive SE**

- Up to 20% of children with SE have NCSE after GCSE
- If child does not begin to respond to painful stimuli within 20 - 30 minutes after tonic clonic SE, suspect nonconvulsive SE
- Urgent EEG

**Definition**

- Nonconvulsive seizure (NCS):
  - Subtle motor symptoms/ coma
  - Electrographic seizures last for at least 10 seconds but less than 30 minutes and meet electrographic criteria
- Nonconvulsive status epilepticus (NCSE):
  - Subtle motor symptoms/ coma
  - Electrographic seizures last at least 30 minutes
**EEG criteria for NCS:**

Young GB et al. Neurology 1996;47:83-89

Any pattern lasting at least 10 seconds satisfying any one of the following 3 primary criteria:

**Primary criteria:**
1. Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at > 3/sec.
2. Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at < 3/sec and the secondary criterion.
3. Sequential rhythmic, periodic, or quasi-periodic waves at > 1/sec and unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/sec, e.g., from 2 to 3/sec) or location (gradual spread into or out of a region involving at least 2 electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not adequate to satisfy evolution in morphology.

**Secondary criterion:**
Significant improvement in clinical state or appearance of previously-absent normal EEG patterns (such as a posterior dominant rhythm) temporally coupled to acute administration of a rapidly-acting antiepileptic drug. Resolution of the “epileptiform” discharges leaving diffuse slowing without clinical improvement and without appearance of previously-absent normal EEG patterns would not satisfy the secondary criterion.

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**Type of SE: seminology**

**Absence SE: symptoms**

**Typical:** prolonged confusion and drowsy with typical EEG abnormalities

**Occasional:** agitation, violent behavior and hallucination

**Remark:** automatisms, blinking, and jerks of the face and limbs might be observed, thereby generating an overlap between absence SE and myoclonic SE

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**Absence SE: EEG findings**

Continuous, generalized 3 Hz spike-and-wave discharges with rhythmic slowing, spike-and-slow waves, polyspikes and diffuse background slowing

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**Complex partial SE**

**Definition:** recurrent complex partial seizures without full recovery of consciousness between seizures OR continuous “epileptic twilight state” with cycling between unresponsive and partially responsive phases.

**Typical:** automatisms, bizarre behavior, amnesia, aphasia

**Remark:** Differentiation of complex partial SE from absence SE is difficult to achieve on clinical grounds alone.
NCSE in coma

**Typical:** prolonged confusion and drowsy with typical EEG abnormalities

**Occasional:** agitation, violent behavior and hallucination

**Remark:** automatisms, blinking, and jerks of the face and limbs might be observed, thereby generating an overlap between absence SE and myoclonic SE.

**EEG criteria for NCSE:**

*Clear-cut criteria:*

- Frequent or continuous focal electrographic seizures with ictal patterns that change in amplitude, frequency or localization
- Frequent or continuous generalized spike-and-waves in patients without a prior history of epilepsy
- Frequent or continuous generalized spike-and-waves, significantly different in amplitude or frequency as compared to previous findings, in patients with a history of epileptic encephalopathy
- Periodic lateralized epileptiform discharges (PLEDs) in comatose patients after convulsive status epilepticus

*Equivocal patterns:*

- Frequent or continuous electroencephalographic abnormalities in patients with acute cerebral injuries whose electroencephalograms showed no previous similar finding
- Frequent or continuous generalized spike-and-waves, not significantly different in amplitude or frequency as compared to previous findings, in patients with a history of epileptic encephalopathy whose clinical symptoms suggest nonconvulsive status epilepticus

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**Benzodiazepine trial for diagnosis of NCSE:**

Appropriate patients have rhythmic or periodic focal or generalized epileptiform discharges on EEG with unexplained altered level of consciousness or a level of consciousness lower than expected given their level of sedation. Patients who are heavily sedated/paralyzed are not suitable as they would not be expected to demonstrate clinical improvement.

### Periodic lateralized epileptiform discharges (PLEDs)

#### PLEDs proper
- Repetitive periodic sharp-and-slow waves with 1-1.5 seconds in interval over left temporal area

#### BIPLEDs

#### GPEDs

#### GPEDs proper

#### SIRPIDs

### Benzodiazepine trial for diagnosis of NCSE:

- Sequential small doses of rapidly acting short-duration benzodiazepine such as midazolam at 1 mg/dose
- Between doses, repeated clinical and EEG assessment
- Trial is stopped after any of the following:
  1. Persistent resolution of the EEG pattern (and exam repeated)
  2. Definite clinical improvement
  3. Respiratory depression, hypertension, or other adverse effect
  4. A maximum dose is reached (such as 0.2 mg/kg midazolam, although higher may be needed if the patient is on chronic benzodiazepines)

Test is considered positive if there is resolution of the potentially ictal EEG pattern and either an improvement in the clinical state and an appearance of previously absent normal EEG patterns (e.g. posterior dominant “alpha” rhythms). If EEG improves but patient does not, the result is equivocal.

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**PLEDs: Area of uncertainty**

![Diagram of PLEDs types]

- **PLEDs**
  - PLEDs proper
  - PLEDs plus
- **BIPLEDs**
- **GPEDs**
  - GPEDs proper
  - GPEDs plus
  - GPEDs proper
**PLEDs plus**
- Repetitive periodic sharp-and-slow waves with irregular intervals (0.5 - 3 seconds)

**BiPLEDs**
- Bilaterally independent sharp waves, spike-wave over bi-temporal areas

**GPEDs**
- Rhythmic, bilateral, synchronous, high amplitude sharp waves with suppression patterns

**PLEDs: Area of uncertainty**

<table>
<thead>
<tr>
<th>PLEDs</th>
<th>BiPLEDs</th>
<th>PSIDs</th>
<th>PLIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-discharge interval</td>
<td>Typical 0.5 to 4 s, up</td>
<td>Typical 5.5 to 4 s, up</td>
<td>3 - 4 s</td>
</tr>
<tr>
<td>Topography</td>
<td>Lateralized</td>
<td>Lateralized</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Rate of onset of interictal seizures</td>
<td>High, approximately</td>
<td>High, approximately</td>
<td>Variable</td>
</tr>
<tr>
<td>Typical interictal &gt; 40 s, idiosyncratic</td>
<td>Typical interictal &gt; 40 s, idiosyncratic</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Area of onset</td>
<td>Bilateral</td>
<td>Bilateral</td>
<td>Bilateral</td>
</tr>
</tbody>
</table>

**The Ictal-Interictal-Injury Continuum**

**PLEDs: Are they ictal discharges?**

- **PROs**
  - Correlation with clinically focal motor jerking
  - PET/CT study: increased regional glucose metabolism
  - SPECT: increased regional cerebral perfusion that normalized when the PLEDs resolved
  - In elderly, some have been associated with confusional state that resolved spontaneously or with DZP treatment

- **Cons**
  - Found in children with chronic diffuse brain lesions without clinical seizure (inter-ictal discharges)
  - Found in patient after elimination of convulsive SE (post-ictal discharges)
**Initial investigations**

- Labs
  - Electrolytes
  - Ca, Mg, PO₄, glucose
  - CBC
  - Liver function tests, ammonia
  - Anticonvulsant level
  - Toxicology

- Lumbar puncture
  - Always defer LP in unstable patient, but never delay antibiotic/antiviral rx if indicated

- CT scan
  - Indicated for focal seizures or deficit, history of trauma or bleeding d/o

**Treatment**

- A Oxygen, oral airway. Avoid hypoxia!

- B Consider bag-valve mask ventilation. Consider intubation

- C IV/IO access. Rx. hypotension, but **NOT** hypertension

- D Anticonvulsants

- **Give glucose** (2-4 ml/kg D25%, infants 5 ml/kg D10%), unless normo- or hyperglycemic

- **Hyperglycemia has no negative effect in SE** (as long as significant hyperosmolality is being avoided)

**Guideline for Management of SE in Infant (age > 1 month), Children and Adolescents**

- Applicable to the ER, clinical wards or in the ICU.
- Most seizures in childhood stop within five minutes.
- **Definition of status epilepticus**: ongoing or recurrent for more than 30 min, in practice treatment should start if the seizure has not spontaneously terminated after five minutes.
- The times of drug administration in the guidelines are from time of seizure onset, or if historically unclear, time of arrival in the ER.
- **Resuscitate**: A - support airway
  - B - administer 100% oxygen, assess ventilation
  - C - check pulse, cardiac monitor, establish IV access

- **Investigations**: glucose, electrolytes, Ca, Mg, blood gas, other as indicated
- **Diagnosis**: a Management of Underlying Cause

- The longer you wait with anticonvulsant, the more anticonvulsant you will need to stop SE

- Most common mistake is ineffective dose
### Guideline for Management of SE in Infant (age > 1 month), Children and Adolescents
(revised July 2009)

#### Refractory status epilepticus (RSE): ongoing guidelines after acute presentation

<table>
<thead>
<tr>
<th>Time From Seizure Onset</th>
<th>Drug/Dosage/Method of Administration</th>
<th>Time from Seizure Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 min.</td>
<td>Midazolam IV infusion</td>
<td>1 hr 45 min.</td>
</tr>
<tr>
<td></td>
<td>- bolus 0.2 mg/kg (max 10 mg) then initiate infusion at 0.1 mg/kg/h (or 2 microgram/kg/min)</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- infusion rate: 0.1 mg/kg/h or 2 microgram/kg/min</td>
<td>1 hr 45 min.</td>
</tr>
<tr>
<td></td>
<td>- discontinue midazolam &amp; phenobarbital once infusion started</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- maintain phenytoin at therapeutic level</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- consider vasopressor support</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- based on EEG suppression of epileptiform discharges, use additional boluses of 2 mg/kg followed by increase in infusion rate of 1 mg/kg/h every 30 minutes to 6 mg/kg/h as needed</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- in addition, consider NG topiramate, NG or IV valproic acid or NG or IV levetiracetam.</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- if no seizures for 48 h</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- taper thiopentone over 12 hr in 25 percent decrements</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- re-institute phenobarbital while tapering</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- Therapy will be individualized at this stage in consultation between ICU and Neurology.</td>
<td>45 min.</td>
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<tr>
<td></td>
<td>- Consider Propofol (1-2 mg/kg) or Vecuronium IV bolus if clinically indicated.</td>
<td>45 min.</td>
</tr>
<tr>
<td></td>
<td>- EEG monitoring absolutely requires before giving muscle relaxant.</td>
<td>45 min.</td>
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</table>

#### Established SE

<table>
<thead>
<tr>
<th>Time From Seizure Onset</th>
<th>Drug/Dosage/Method of Administration</th>
<th>Time from Seizure Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min. (Initial RSE)</td>
<td>Levetiracetam or Valproic acid</td>
<td>10 min.</td>
</tr>
<tr>
<td></td>
<td>- IV at 5 mg/kg/hr max 1 g</td>
<td>10 min.</td>
</tr>
<tr>
<td></td>
<td>- in children under 18 months, consider pyridoxine 100 mg IV push</td>
<td>10 min.</td>
</tr>
<tr>
<td>5-10 min. (Established SE)</td>
<td>Midazolam IV infusion</td>
<td>10 min.</td>
</tr>
<tr>
<td></td>
<td>- bolus 0.2 mg/kg (max 10 mg) then initiate infusion at 0.1 mg/kg/h (or 2 microgram/kg/min)</td>
<td>10 min.</td>
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