Management of acute seizure and status epilepticus

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Division of Neurology
Ramathibodi hospital
Outlines

• Seizure cluster/ Acute repetitive seizures

• Status epilepticus
Seizure cluster
• A 45-yo male with past medical history of brain tumor s/p partial tumor removal presented to the outpatient clinic with chief complaint of frequent and repetitive focal seizures with preserved awareness for a day. Each seizure was characterized by left face clonic with preserved awareness, lasting for two hours. He had experienced seizure clusters, 4 times a day. He had one GTCs.
Definition of epileptic seizure by the International League Against Epilepsy (ILAE)

• An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Epilepsia, 46(4):470–472, 2005
Acute Repetitive Seizures (ARS)

• The practical definition of acute repetitive seizures has not been established.

• Acute repetitive seizures is neurologic emergency and a common clinical phenomenon describing an increase in seizures occurring over a specific period of time (ranging from several minutes up to 24 hours).

• Acute repetitive seizures may include any type of seizure and may vary in severity, but by definition there is complete recovery in between seizures.

Curr Opin Neurol 2015;28(2):143Y150.
Oral tablet benzodiazepine

- Lorazepam
- Clonazepam
- Clobazam

<table>
<thead>
<tr>
<th>Clonazepam</th>
<th>Rivotril tab 0.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivotril tab 2 mg</td>
</tr>
<tr>
<td></td>
<td>Prenarpil tab 0.5 mg</td>
</tr>
<tr>
<td></td>
<td>Prenarpil tab 1 mg</td>
</tr>
<tr>
<td></td>
<td>Prenarpil tab 2 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clobazam</th>
<th>Frisium 5 mg</th>
</tr>
</thead>
</table>
Outpatient acute benzodiazepine therapy

• Rectal diazepam is the only currently marketed treatment available for use by nonmedical caregivers in the USA, and buccal midazolam is approved in the European Union.
# Outpatient acute benzodiazepine therapy

<table>
<thead>
<tr>
<th>Medications</th>
<th>Formulation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>oral tablet</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(FDA approved)</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>intramuscular</td>
<td>The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) in pre-hospital status epilepticus</td>
</tr>
<tr>
<td></td>
<td>buccal</td>
<td></td>
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<tr>
<td></td>
<td>intranasal</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>oral tablet</td>
<td></td>
</tr>
<tr>
<td></td>
<td>intranasal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sublingual</td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>cyclic natural progesterone</td>
<td>catamenial epilepsy Neurology 2014; 83:345–348.</td>
</tr>
</tbody>
</table>
Management of acute repetitive seizures (ARS)

• Diagnosis of seizure clusters

• Identify the etiology of ARS

• Benzodiazepines remain the mainstay of therapy in ARS. The treatment of ARS includes the usage of extra doses of usual antiepileptic medications and oral benzodiazepines (diazepam or lorazepam) for mild ARS.

• Educating the patient and families about seizure first aid and the use of rescued anti-seizure medications.
Status epilepticus (SE)
Status epilepticus

• Status epilepticus (SE) is a neurologic emergency with high morbidity and mortality. It represents the persistence of abnormal excitation and the ineffective recruitment of inhibition.

• The management of SE requires immediate action and diligence to avoid pharmacoresistance and brain injury.
Old definition of SE

- A definition of more than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between was widely adopted, citing neuronal damage in animal models beyond this timeframe.
## Phase 1: compensation

<table>
<thead>
<tr>
<th>Cerebral changes</th>
<th>Systemic and metabolic changes</th>
<th>Autonomic and cardiovascular changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>increased cerebral blood flow</td>
<td>hyperglycemia</td>
<td>increased blood pressure</td>
</tr>
<tr>
<td>increased cerebral metabolism</td>
<td>lactic acidosis</td>
<td>increased cardiac output</td>
</tr>
<tr>
<td>increased lactate concentration</td>
<td></td>
<td>massive catecholamine release</td>
</tr>
<tr>
<td>increased glucose concentration</td>
<td></td>
<td>cardiac dysthymia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>urine incontinence</td>
</tr>
</tbody>
</table>
## Phase 2: decompensation

<table>
<thead>
<tr>
<th>Cerebral changes</th>
<th>Systemic and metabolic changes</th>
<th>Autonomic and cardiovascular changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>failure of cerebral autoregulation</td>
<td>hypoglycemia</td>
<td>hypoxia</td>
</tr>
<tr>
<td>hypoxia</td>
<td>hypokalemia/hyperkalemia</td>
<td>falling blood pressure</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>metabolic and respiratory acidosis</td>
<td>falling cardiac output</td>
</tr>
<tr>
<td>increased intracranial pressure and cerebral oedema</td>
<td>hepatic and renal dysfunction</td>
<td>cardiac failure</td>
</tr>
<tr>
<td></td>
<td>consumptive coagulopathy</td>
<td>respiratory failure</td>
</tr>
<tr>
<td></td>
<td>DIC</td>
<td>hyperpyrexia</td>
</tr>
<tr>
<td></td>
<td>rhabdomyolysis, myoglobinuria</td>
<td></td>
</tr>
</tbody>
</table>
A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, †Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer,
††Shlomo Shinnar, †‡Simon Shorvon, and §§Daniel H. Lowenstein

Epilepsia, 56(10):1515–1523, 2015
doi: 10.1111/epi.13121

SUMMARY

The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) have charged a Task Force to revise concepts, definition, and classification of status epilepticus (SE). The proposed new definition of SE is as follows: Status epilepticus 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 t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures. This definition is conceptual, with two operational dimensions: the first is the length of the seizure and the time point (t1) beyond which the seizure should be regarded as “continuous seizure activity.” The second time point (t2) is the time of ongoing seizure activity after which there is a risk of long-term consequences. In the case of convulsive (tonic–clonic) SE, both time points (t1 at 5 min and t2 at 30 min) are based on animal experiments and clinical research. This evidence is incomplete, and there is furthermore considerable variation, so these time points should be considered as the best estimates currently available. Data are not yet available for other forms of SE, but as knowledge and understanding increase, time points can be defined for specific forms of SE based on scientific evidence and incorporated into the definition, without changing the underlying concepts. A new diagnostic classification system of SE is proposed, which will provide a framework for clinical diagnosis, investigation, and therapeutic approaches for each patient. There are four axes: (1) semiology; (2) etiology; (3) electroencephalography (EEG) correlates; and (4) age. Axis 1 (semiology) lists different forms of SE divided into those with prominent motor systems, those without prominent motor systems, and currently indeterminate conditions (such as acute confusional states with epileptiform EEG patterns). Axis 2 (etiology) is divided into subcategories of known and unknown causes. Axis 3 (EEG correlates) adopts the latest recommendations by consensus panels to use the following descriptors for the EEG: name of pattern, morphology, location, time-related features, modulation, and effect of intervention. Finally, axis 4 divides age groups into neonatal, infancy, childhood, adolescent and adulthood, and elderly.

KEY WORDS: Status epilepticus, Seizure, Definition, Classification, Seizure duration.
<table>
<thead>
<tr>
<th>Type of SE</th>
<th>Operational dimension 1</th>
<th>Operational dimension 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (t1), when a seizure is likely to be prolonged leading to continuous seizure activity</td>
<td>Time (t2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)</td>
</tr>
<tr>
<td>Tonic-clonic SE</td>
<td>5 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Focal SE with impaired consciousness</td>
<td>10 min</td>
<td>&gt; 60 min</td>
</tr>
<tr>
<td>Absence status epilepticus</td>
<td>10-15 min(^a)</td>
<td>unknown</td>
</tr>
</tbody>
</table>

\(^a\): Evidence for the time frame is currently limited and future data may lead to modifications.
Classification of SE

• 1 Semiology

• 2 Etiology

• 3 EEG correlates

• 4 Age
Axis 1: Semiology

- The presence or absence of prominent motor symptoms
- The degree (qualitative or quantitative) of impaired consciousness
Axis 1: Semiology

A) With prominent motor symptoms

A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
   A.1.a. Generalized convulsive
   A.1.b. Focal onset evolving into bilateral convulsive SE
   A.1.c. Unknown whether focal or generalized

A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
   A.2.a. With coma
   A.2.b. Without coma

A.3 Focal motor
   A.3.a. Repeated focal motor seizures (Jacksonian)
   A.3.b. Epilepsia partialis continua (EPC)
   A.3.c. Adverse status
   A.3.d. Oculoclone status
   A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 Tonic status

A.5 Hyperkinetic SE
Axis 1: Semiology

(B) Without prominent motor symptoms (i.e., non-convulsive SE, NCSE)

B.1 NCSE with coma (including so-called “subtle” SE)

B.2 NCSE without coma
   B.2.a. Generalized
      B.2.a.a Typical absence status
      B.2.a.b Atypical absence status
      B.2.a.c Myoclonic absence status
   B.2.b. Focal
      B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
      B.2.b.b Aphasic status
      B.2.b.c With impaired consciousness

B.2.c Unknown whether focal or generalized
   B.2.c.a Autonomic SE
Axis 2: Etiology

• Known (i.e., symptomatic)
  - Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
  - Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
  - Progressive (e.g., brain tumor, Lafora’s disease and other PMEs, dementias)
  - SE in defined electroclinical syndromes

• Unknown (i.e., cryptogenic)
Axis 3: Electroencephalographic correlates

- Currently there are no evidence-based EEG criteria for SE.
EEG patterns in SE

1. Location: generalized (including bilateral synchronous patterns), lateralized, bilateral independent, multifocal.

2. Name of the pattern: Periodic discharges, rhythmic delta activity or spike-and-wave/sharp- and-wave plus subtypes.

3. Morphology: sharpness, number of phases (e.g., triphasic morphology), absolute and relative amplitude, polarity.

4. Time-related features: prevalence, frequency, duration, daily pattern duration and index, onset (sudden vs. gradual), and dynamics (evolving, fluctuating, or static).


6. Effect of intervention (medication) on EEG.
Axis 4: Age

1. Neonatal (0 to 30 days)

2. Infancy (1 month to 2 years)

3. Childhood (> 2 to 12 years)

4. Adolescence and adulthood (> 12 to 59 years)

5. Elderly (≥ 60 years)
Management of status epilepticus
Principle of management in patients with SE

1. Stop both ongoing clinical and electrographic seizures

2. Identify and treat the etiology of SE

3. Identify and treat the complications of SE
Choosing the anti-seizure medications

- Age

- Clinical seizure type:
  - CSE and NCSE

- Comorbidities
  - cardiovascular disease
  - liver disease
  - kidney disease

- History of drug allergy
  - minor rash to SJSs

- Anti-seizure medications
  - administration
  - mechanism of action
  - pharmacodynamics
  - pharmacokinetics
  - efficacy for seizure type
  - recommended doses
  - adverse effects
  - drug interactions
Convulsive status epilepticus (CSE)
Definition of CSE

• CSE is a convulsive seizure lasting more than 5 min or consecutive seizures without recovery of consciousness.

• In the case of convulsive SE, both time points (t1 at 5 min and t2 at 30 min) are based on animal experiments and clinical research.
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<sup>a</sup> Evidence for the time frame is currently limited and future data may lead to modifications
Time is the brain!

- The response to AEDs treatment is decreasing with time and ongoing seizures probably due to the following reasons;

  - Functional GABA receptors are decreased due to internalization of GABA receptors.

  - NMDA receptors are up-regulated. This can resulted in calcium influx intracellularly which makes seizure control more difficult and may causes cellular damage and secondary brain injury.

  - There is the upregulation of drug-efflux transporters such as P- glycoprotein.

  - Ongoing status can resulted in an increment of pro-inflammatory agents.
Conclusions

As initial intravenous treatment for overt generalized convulsive status epilepticus, lorazepam is more effective than phenytoin. Although lorazepam is no more efficacious than phenobarbital or diazepam and phenytoin, it is easier to use.
Established Status Epilepticus Treatment Trial (ESETT)

- **Full title:** A Multicenter, Randomized, Blinded, Comparative Effectiveness Study of Fosphenytoin, Valproic Acid, or Levetiracetam in the Emergency Department Treatment of Patients With Benzodiazepine-refractory Status Epilepticus

- Estimated study completion date: in July 2020
Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society
FIGURE 1. Proposed treatment algorithm for status epilepticus.

Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytical framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.
Treatment phases of CSE

• Stage 1 (early or impending CSE)

  - Benzodiazepines are the drugs of choice.

  - RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) IV lorazepam vs IM midazolam*

  - AES guideline state that IM midazolam has a superior effectiveness compared to intravenous lorazepam in adults with CSE without established intravenous access (Level A)**

Treatment phases of CSE

• **Stage 2 (Established SE):** CSE persisting after first-line treatments

  - phenytoin (fosphenytoin)
  - phenobarbital
  - valproic acid
  - levetiracetam
  - lacosamide
Treatment phases of CSE

- **Stage 3 (refractory CSE):** CSE persisting > 60 minutes after second-line treatments

  - Anesthetic agents are the drugs of choice for the treatment of refractory CSE.
**Midazolam**

<table>
<thead>
<tr>
<th>Loading dose</th>
<th>Initial rate</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam 0.2 mg/kg IV over 2 to 5 minutes; repeat 0.2 to 0.4 mg/kg boluses every 5 minutes until seizures stop, up to a maximum loading dose of 2 mg/kg</td>
<td>0.1 mg/kg/hr</td>
<td>0.05 to 2.9 mg/kg/hour</td>
</tr>
</tbody>
</table>

**Mechanism of action of midazolam**

- GABA-A agonists

<table>
<thead>
<tr>
<th>Onset of action</th>
<th>3-5 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life elimination</td>
<td>3 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>hepatic CYP3A4</td>
</tr>
<tr>
<td>Excretion</td>
<td>urine</td>
</tr>
</tbody>
</table>

**Dosing: hepatic impairment**

- no data; use with caution

**Dosing: renal impairment**

- no data; use with caution

**Adverse effects**

- respiratory and cardiovascular depression
- development of tachyphylaxis with prolonged infusions
**Propofol**

<table>
<thead>
<tr>
<th></th>
<th>Loading dose</th>
<th>Initial rate</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propofol</strong></td>
<td>1 to 2 mg/kg IV over 3 to 5 minutes; repeat boluses every 3 to 5 minutes until seizures stop, up to maximum total loading dose of 10mg/kg</td>
<td>20 microgram/kg/min; bolus and increase rate until seizure control</td>
<td>30 to 200 microgram/kg/min titrated to EEG with 5 to 10 microgram/kg/min every 5 minutes or 1 mg/kg bolus for breakthrough status epilepticus</td>
</tr>
</tbody>
</table>

**Mechanism of action of propofol**

- GABA-A agonists, N-methyl-D-aspartate (NMDA) antagonist

**Onset of action**

- 30 seconds

**Half-life elimination**

- 40 minutes- 7 hours

**Metabolism**

- hepatic

**Excretion**

- urine

**Dosing: hepatic impairment**

- no dosage adjustment necessary

**Dosing: renal impairment**

- no dosage adjustment necessary

**Adverse effects**

- respiratory and cardiovascular depression,
  - “propofol infusion syndrome,” which includes potentially fatal myocardial failure with lactic acidosis, hypertriglyceridemia, and rhabdomyolysis
**Thiopental**

<table>
<thead>
<tr>
<th></th>
<th>Loading dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiopental</strong></td>
<td>100-250 mg IV drip &gt; 20 seconds then 50 mg IV every 2-3 minutes until seizure was stopped.</td>
<td>3-5 mg/kg/hour</td>
</tr>
</tbody>
</table>

**Mechanism of action of thiopental**

<table>
<thead>
<tr>
<th></th>
<th>GABA-A agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of action</strong></td>
<td>30 seconds</td>
</tr>
<tr>
<td><strong>Half-life elimination</strong></td>
<td>5-22 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>hepatic, primary to inactive metabolites</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>urine, primary to inactive metabolites</td>
</tr>
<tr>
<td><strong>Dosing: hepatic impairment</strong></td>
<td>no data</td>
</tr>
<tr>
<td><strong>Dosing: renal impairment</strong></td>
<td>no data</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>dose-dependent respiratory and cardiovascular depression, long recovery time, immunosuppression</td>
</tr>
</tbody>
</table>
**Ketamine**

<table>
<thead>
<tr>
<th>Loading dose</th>
<th>Initial rate</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>1 to 4.5 mg/kg with supplements of 0.5-2.5 mg/kg every 30-45 minutes or 10 to 50 microgram/kg/min</td>
<td>1.5 mg/kg every 3 to 5 minutes until seizures stops, up to a maximum of 4.5 mg/kg</td>
</tr>
</tbody>
</table>

**Mechanism of action of ketamine**
- N-methyl D-aspartate (NMDA) receptor antagonists

**Onset of action**
- 30 seconds

**Half-life elimination**
- 2.5 hours

**Metabolism**
- Hepatic via CYP3A4

**Excretion**
- Urine

**Dosing: hepatic impairment**
- No data

**Dosing: renal impairment**
- No data

**Adverse effects**
- Elevation of blood pressure, increased intracranial pressure
## Topiramate

<table>
<thead>
<tr>
<th></th>
<th>Loading dose</th>
<th>Maintenance dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topiramate</strong></td>
<td>100 mg PO q 12 hours</td>
<td>400-800 mg/day q 12 hours</td>
<td>metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>topiramate+propofol → refractory acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>topiramate+ sodium valproate → hyperammonemia</td>
</tr>
</tbody>
</table>

### Mechanism of action of topiramate
- Blockade of the ionotropic glutamatergic AMPA/kainate receptors
- Blocks neuronal voltage-dependent sodium channels
- Enhancement of GABAergic activity

### Onset of action
- 2-4 hours

### Half-life elimination
- 20 hours

### Metabolism
- Minor amounts metabolized in liver

### Excretion
- Urine 70%

### Dosing: hepatic impairment
- No data; use with caution in patient with severe hepatic impairment

### Dosing: renal impairment
- Reduce dose to 50% if CrCl < 70

### Adverse effects
- Drowsiness, metabolic acidosis, hyperammonemia

### Topiramate tablet formulations
- **Topamax tab 25 mg** (film-coated)
- **Topamax tab 50 mg** (film-coated)
- **Topamax tab 100 mg** (film-coated)
Refractory status epilepticus (RSE)

• Quick check lists

  - The patient must be intubated and should be admitted in the intensive care unit for respiratory monitoring, and hemodynamic monitoring.

  - Continuous electroencephalography (cEEG) monitoring is critical during the treatment of RSE and should be performed in every patient with RSE (if possible).
cEEG monitoring
The usefulness of cEEG monitoring

• cEEG monitoring is necessary to confirm that ongoing seizures have been completely stopped and under controlled after the treatment of RSE.

• Ongoing electrographic seizures may be masked when using paralytics for intubation; therefore patients may continue to seize without any clinical manifestations.

• The depth of anesthesia, the level of CNS suppression, degree of encephalopathy, ongoing electrographic seizures can be assessed by using the cEEG monitoring. Thus, the information from cEEG monitoring is very useful for the treatment of RSE including the adjustment of anti-seizure medications.
Optimal electroclinical endpoint of treatment

• To best of our knowledge, the optimal electroclinical endpoint of treatment has not been studied in a well-designed clinical trials. Therefore, it is uncertain whether the goal should be simple cessation of both clinical and electrographic seizures, or some degree of suppression of cerebral activity.

• Thai clinical practice guideline: no clinical and electrographic seizures plus burst suppression with interburst interval of 5-15 seconds for 24 hours.

http://thaiepilepsysociety.com/
Burst suppression with interburst intervals of 3 seconds
Burst suppression with interburst intervals of 5 seconds
Tapering off anesthetic agents in patient with RSE

- **Thai clinical practice guideline:** no clinical and electrographic seizures for 24-48 hours.

- Before tapering off anesthetic agent, it is critical that high therapeutic levels of at least one longer-acting anti-seizure medication be maintained before tapering continuous infusions.

  - avoid anti-seizure medications with a primarily GABAergic mechanism

  - avoid > 2 anti-seizure medications

  - try anti-seizure medications with multiple mechanisms of action and low drug interactions

http://thaiepilepsysociety.com/
Tapering off anesthetic agents in patient with RSE

• When electrographic seizures re-appear during tapering off anesthetic agent, most experts recommend to re-treat with higher doses of the anesthetic agent, or for longer at doses that were successful earlier. Additional anti-seizure medications should be immediately prescribed before considering the next attempt.
Treatment phases of CSE

• **Stage 4 (super-refractory CSE)***: CSE persisting for more than 24 hours after administration of third-line treatments

  - anesthetic agents
  - ketamine
  - immunomodulatory therapy
  - hypothermia
  - new anti-seizure medications
  - ketogenic diet*

*Brain 2011;134:2802–18.
Perampanel (PER)

• PER has a novel mechanism of action. It is a first in class orally active, selective, non-competitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor agonist.

• PER
  - initial dose in case small case series: 2-32 mg
  - adult patients with refractory and super-refractory status epilepticus in a neurological intensive care unit
<table>
<thead>
<tr>
<th>Perampanel</th>
<th>Fycompa tab 2 mg (film-coated)</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fycompa tab 4 mg (film-coated)</td>
<td>114.25</td>
</tr>
<tr>
<td></td>
<td>Fycompa tab 8 mg (film-coated)</td>
<td>195.75</td>
</tr>
</tbody>
</table>
Focal motor status epilepticus
Epilepsia partialis continua (EPC)

• Treatment

- identify and treat causal or precipitating factors

- anti-seizure medications

  - first-generation: carbamazepine, valproate, clonazepam

  - second-generation: topiramate, levetiracetam
Non-convulsive status
Non-convulsive status epilepticus (NCSE)

• Positive symptoms
  - agitation, aggression, delirium, psychosis
  - facial twitching, automatisms
  - sustained eye deviation, nystagmus

• Negative symptoms
  - aphasia
  - mutism
  - eye staring
  - confusion, lethargy, coma
Non-convulsive status epilepticus (NCSE)

• Patients with NCSE may have no clinical signs or develop only subtle jerks of the face, eyes, and extremities.

• NCSE is diagnosed only by electroencephalography (EEG).
Salzburg EEG consensus criteria for non-convulsive status epilepticus (SCNC)

<table>
<thead>
<tr>
<th>Patients without known epileptic encephalopathy</th>
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</thead>
<tbody>
<tr>
<td>• EDs &gt; 2.5 Hz, or</td>
</tr>
<tr>
<td>• EDs ≤ 2.5 Hz or rhythmic delta/theta activity (&gt; 0.5Hz) AND one of the following:</td>
</tr>
<tr>
<td>- EEG and clinical improvement after IV AED*, or</td>
</tr>
<tr>
<td>- Subtle clinical ictal phenomena, or</td>
</tr>
<tr>
<td>- Typical spatiotemporal evolution**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with known epileptic encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increase in prominence or frequency when compared to baseline with observable change in clinical state</td>
</tr>
<tr>
<td>• Improvement of clinical and EEG* features with IV AEDs</td>
</tr>
</tbody>
</table>

* If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE.

** Increment onset(increase in voltage and change in frequency), or evolution in pattern(change in frequency > 1Hz or change in location), or decrementing termination(voltage and frequency).

EDs: epileptiform discharges(spikes, polyspikes, sharp-waves, sharp-and-wave complexes)
IV AED: intravenous antiepileptic drugs
Management of NCSE

• The aggressiveness of anti-seizure medication treatment should be individualized on each patient with NCSE. The following variables should be considered:

  - degree of impairment of consciousness

  - etiology
NCSE without coma

• For NCSE patients without coma, we suggest treatment with an IV benzodiazepine combined with an IV noncoma-inducing anti-seizure medications (AEDs).

• Noncoma-inducing AEDs
  - phenytoin
  - sodium valproate
  - levetiracetam
  - lacosamide
NCSE with coma

• In the critically ill coma population, there is considerable controversy about whether to treat NCSE as aggressively as convulsive status epilepticus.
Refractory nonconvulsive status epilepticus

- Refractory status epilepticus (RSE) refers to status epilepticus that continues despite administration of therapeutic doses of two or more anti-seizure drugs.

- Treatment of refractory NCSE must be individualized. Examples of situations that may warrant aggressive therapy include subtle status epilepticus developing from generalized convulsive seizures, NCSE with acute brain injury, an cryptogenic new-onset refractory status epilepticus (NORSE).
• NORSE is a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause.
NCSE with coma
American Clinical Neurophysiology Society’s Standardized Critical Care EEG Terminology: 2012 version
Postanoxic status epilepticus (PSE)

- Thai epilepsy society (http://thaiepilepsysociety.com/epilepsy-digest-2017-issue-1-jan-april/)

Postanoxic seizures

Pathophysiology of clinical and electrographic seizures in postanoxic encephalopathy

An Official Journal of Epilepsy Society of Thailand

Issue 1: January-April
The end