Status epilepticus és kezelése

Dr. Szok Délia

SZTE ÁOK Neurológiai Klinika
Szeged
http://www.epilepszia.hu/
Status epilepticus (SE)

• A medical and neurological emergency with significant potential morbidity and mortality

• Management of SE is aimed at:
  1. stabilization and avoidance of secondary injury
  2. rapid identification/diagnosis
  3. rapid and adequate control of seizures (anticonvulsive therapy)
  4. rapid treatment of the etiology of SE (causal therapy)
Epidemiology of SE

**Incidence:** 10-40/100,000 persons/year
- Convulsive (gen.) SE: 3.6-6.6/100,000
- Non-convulsive SE: 2.6-7.8/100,000

**Age:** <1 year and 60< year

**Treatment response:**
- Refractory SE: 23-43% of all SEs
- Superrefractory SE: 15% of convulsive SEs

**Mortality:** 3-33%
- TBI with cerebral contusion: mortality due to NCSE is high!
History of SE

• Trousseau (1867):
  “In the \textit{status epilepticus}, when the \textit{convulsive}(!) condition is almost \textit{continuous}, \textit{something special} takes place which requires an explanation.”

• ILAE (International League Against Epilepsy) (1970)

• ILAE (1981)

• ILAE (2015)
Definition of SE

The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) Task Force

- The proposed new definition of SE is as follows:
  - **Status epilepticus (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 t1).

SE 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.

Trinka et al *Epilepsia* 2015;56(10):1515-1523.
Definition of SE

- This definition is conceptual, with 2 operational dimensions:
  
  1. the first is the length of the seizure and the time point \((t_1)\) beyond which the seizure should be regarded as "continuous seizure activity"
  
  2. the second time point \((t_2)\) is the time of ongoing seizure activity after which there is a risk of long-term consequences (including neuronal death, neuronal injury, alteration of neuronal networks)

In the case of convulsive (tonic-clonic) SE:

  both time points \((t_1 \text{ at } 5 \text{ min and } t_2 \text{ at } 30 \text{ min})\) are based on animal experiments and clinical research.

  (This evidence is incomplete, so these time points should be considered as the best estimates currently available.)
Nota bene!

Nota bene:

• The *first* seizure can be SE!

• More than 10% of *first* unprovoked seizures last longer than 30 min
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 4 axes:

1. Semiology
2. Etiology
3. EEG correlates
4. Age
Classification of SE

• Axis 1: Semiology
  • different forms of SE:
    – with or without prominent motor symptoms
    – the degree (qualitative or quantitative) of impaired consciousness
    – currently indeterminate conditions
      (such as acute confusional states with epileptiform EEG patterns)

• Axis 2: Etiology
  • known (symptomatic) and unknown (cryptogenic) causes

• Axis 3: EEG correlates
  • name of EEG pattern, morphology, location, time-related features, modulation, and effect of intervention (medication)

• Axis 4: Age groups
  • neonatal  (0 to 30 days)
  • infancy    (1 month to 2 years)
  • childhood  (2 to 12 years)
  • adolescence and adulthood (12 to 59 years)
  • elderly    (>60 years)
Nota bene!

- At least **half (50%)** of the patients with SE **do not** have epilepsy (or specific epilepsy syndromes), they have SE due to **acute or chronic** central nervous system (CNS) or systemic (not-CNS) illness.
## Operational dimensions

<table>
<thead>
<tr>
<th>Type</th>
<th>t1</th>
<th>t2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic-clonic SE (motor)</td>
<td>5 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Focal SE (motor or non-motor)</td>
<td>10 min</td>
<td>&gt;60 min</td>
</tr>
<tr>
<td>Absence SE (non-motor; NCSE)</td>
<td>10-15 min</td>
<td>unknown</td>
</tr>
</tbody>
</table>
Axis 1: Semiology of SE

A) With prominent motor symptoms

A.1 Convulsive SE (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 SE
   A.3.a. Repeated focal motor seizures (Jacksonian)
   A.3.b. Epilepsia partialis continua (Kojevnikov)
   A.3.c. Adversive status
   A.3.d. Oculoclonic status
   A.3.e. Ictal paresis (i.e. focal inhibitory SE)

A.4 Tonic SE
A.5 Hyperkinetic SE

(B) Without prominent motor symptoms (NCSE)

B.1 NCSE with coma
   (e.g. “subtle” SE = refractory GC 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, 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
## Clinical forms of SE

<table>
<thead>
<tr>
<th>Motor</th>
<th>Non-motor (NCSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>Focal</td>
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<tr>
<td></td>
<td>Generalized</td>
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</table>

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<tr>
<th>Motor</th>
<th>Non-motor (NCSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generalized</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal consciousness</th>
<th>Impaired consciousness</th>
<th>Normal consciousness</th>
<th>Impaired consciousness</th>
<th>Normal consciousness</th>
<th>Impaired consciousness</th>
<th>Normal consciousness</th>
<th>Impaired consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplex partial seizures (Jacksonian)</td>
<td>Complex partial seizures (EPC: Kozevnikov)</td>
<td>Myoclonic seizures</td>
<td>GTCSs</td>
<td>Aura continua</td>
<td>Complex partial seizures („dreamy state“)</td>
<td>Absence</td>
<td></td>
</tr>
</tbody>
</table>
Currently indeterminate conditions („Boundary syndromes”)  

- Epileptic encephalopathies  
- Coma with non-evolving epileptiform EEG pattern*  
- Behavioral disturbance (e.g., psychosis) in patients with epilepsy  
- Acute confusional states (e.g., delirium) with epileptiform EEG patterns  

(* Lateralized and generalized periodic discharges with monotonous appearance are not considered as evolving EEG patterns.)
Axis 2: Etiology of SE

1. Known (i.e., symptomatic):
   - Acute
     - stroke, intoxication, malaria, encephalitis, etc.
   - Remote
     - post-traumatic, post-encephalitic, post-stroke, etc.
   - Progressive
     - brain tumor, Lafora’s disease (and other PMEs), dementias
   - SE in defined electroclinical syndromes

2. Unknown (i.e., cryptogenic)
Axis 2: List of etiologies that may cause SE (1-17 categories)

1 Cerebrovascular diseases
2 CNS infections
3 Neurodegenerative diseases
   - Alzheimer’s disease
   - Corticobasal degeneration
   - Frontotemporal dementia
4 Intracranial tumors
5 Cortical dysplasias
6 Head trauma
7 Alcohol-related
   - Intoxication
   - Withdrawal
   - Wernicke encephalopathy
8 Intoxication
   - Drugs
   - Neurotoxins
   - Heavy metals
9 Withdrawal / Low levels of AEDs
10 Cerebral hypoxia/anoxia
11 Metabolic disturbances
   - electrolyte, glucose, acidosis, renal, hepatic
12 Autoimmune disorders
   - Multiple sclerosis (!)
   - Paraneoplastic encephalitis
   - Hashimoto’s encephalopathy
   - Anti-NMDA-R encephalitis
   - Rasmussen encephalitis
   - Cerebral lupus (SLE)
   - TTP (Moschcowitz syndrome)
13 Mitochondrial disorders
   - MELAS, MERFF, Leigh syndrome
14 Chromosomal aberrations and genetic anomalies
15 Neurocutaneous syndromes
16 Hereditaer metabolic disorders
17 Others
   - Familial hemiplegic migraine (FHM) (!)
   - CADASIL
Cortical dysplasias

- Focal cortical dysplasia (FCD) II, tuberous sclerosis complex (TSC), hemimegalencephaly, hemihemimegalencephaly
- Ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor (DNET)
- Periventricular nodular heterotopia (PNH) and other nodular heterotopias
- Subcortical band heterotopia spectrum
- Lissencephaly
- Familial and sporadic polymicrogyria
- Familial and sporadic schizencephaly
- Infratentorial malformations (e.g., dentate dysplasia, mamillary dysplasia, etc.)
Axis 3: EEG correlates of SE

**NB:** None of the ictal EEG patterns of any type of SE is specific. No evidence-based EEG criteria for 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)
5. Modulation:
   - stimulus-induced vs. spontaneous
6. Effect of intervention (medication) on EEG
Axis 4: Age-related electroclinical syndromes of SE

- SE occurring in neonatal and infantile-onset epilepsy syndromes:
  - Tonic status (e.g., in Ohtahara syndrome or West syndrome)
  - Myoclonic status (in Dravet syndrome - SMEI)
  - Focal status
  - Febrile SE

- SE occurring mainly in childhood and adolescence:
  - Autonomic SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)
  - NCSE in specific childhood epilepsy syndromes and etiologies
    - e.g., Ring chromosome 20 and other karyotype abnormalities, Angelman syndrome, Epilepsy with myoclonic-atonic seizures, other childhood Myoclonic encephalopathies
  - Tonic status (in Lennox-Gastaut syndrome)
  - Myoclonic status in progressive myoclonus epilepsies (PME)
  - Electrical status epilepticus in slow wave sleep (ESES)
  - Aphasic status (in Landau-Kleffner syndrome)

- SE occurring mainly in adolescence and adulthood:
  - Myoclonic status in juvenile myoclonic epilepsy (JME)
  - Absence status in juvenile absence epilepsy (JAE)
  - Myoclonic status (in Down syndrome)

- SE occurring mainly in the elderly:
  - Myoclonic status - in Alzheimer’s disease (AD)
  - Non-convulsive status epilepticus (NCSE) - in Creutzfeldt-Jakob disease (CJD)
  - De novo (or relapsing) absence status of later life
Treatment of SE

• is a big challenge
## Treatment of SE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy (IV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Lorazepam</td>
<td>Class I</td>
<td>Level A</td>
</tr>
<tr>
<td>2 Midazolam (IM)</td>
<td>Class I</td>
<td>Level A</td>
</tr>
<tr>
<td>3 Diazepam</td>
<td>Class IIa</td>
<td>Level A</td>
</tr>
<tr>
<td>4 Phenytoin/Fosphenytoin</td>
<td>Class IIb</td>
<td>Level A</td>
</tr>
<tr>
<td>5 Phenobarbital</td>
<td>Class IIb</td>
<td>Level A</td>
</tr>
<tr>
<td>6 Valproate sodium</td>
<td>Class IIb</td>
<td>Level A</td>
</tr>
<tr>
<td>7 Levetiracetam</td>
<td>Class IIb</td>
<td>Level C</td>
</tr>
<tr>
<td><strong>Second-line therapy (IV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Class IIa</td>
<td>Level A</td>
</tr>
<tr>
<td>Phenytoin/Fosphenytoin</td>
<td>Class IIb</td>
<td>Level B</td>
</tr>
<tr>
<td>Midazolam (continuous infusion)</td>
<td>Class IIb</td>
<td>Level B</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Class IIb</td>
<td>Level C</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class IIb</td>
<td>Level C</td>
</tr>
</tbody>
</table>

Hocker SE Continuum (Minneap Minn) 2015  
Brophy GM et al Neurocrit Care 2012
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose/Route</th>
<th>Rate of infusion</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam (Clonazepam)</td>
<td>0.1 mg/kg IV (1 mg/1 ml/amp)</td>
<td>Up to 4 mg per dose in 5-10 min increments</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Midazolam</td>
<td>10 mg IM (5 mg/1 ml/amp)</td>
<td>N/A</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20 mg rectally =2x10mg! rectal solutions 5-30 mg IV push (bolus) ½-3 amp/person</td>
<td>5 mg per dose in 10-15 min increments</td>
<td>Ila</td>
<td>A</td>
</tr>
<tr>
<td>Phenytoin (EPANUTIN® 250 mg á 5 ml)</td>
<td>10-15 mg/kg IV 800-1200 mg/80 kg person 3-5 amp/person</td>
<td>Up to 50 mg/min</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>18-20 mg PE/kg IV</td>
<td>Up to 150 mg/min</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Valproate sodium (CONVULEX® 500 mg á 5 ml)</td>
<td>25-40 mg/kg IV 2000-3200 mg/80 kg person 4-6 amp/person</td>
<td>Up to 3 mg/kg/min</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Levetiracetam (KEPPRA® 500 mg á 5 ml)</td>
<td>2000-4000 mg IV 4-8 amp/person (min. 4 amp.!)</td>
<td>Up to 500 mg/min</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>200-400 mg IV</td>
<td>Infused over 5 min</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
# Treatment of refractory SE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Class, Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam IV</td>
<td>Class IIa, <strong>Level B</strong></td>
</tr>
<tr>
<td>Propofol</td>
<td>Class IIb, Level B</td>
</tr>
<tr>
<td>Pentobarbital/Thiopental</td>
<td>Class IIb, Level B</td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Class IIa, Level B</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class IIb, <strong>Level C</strong></td>
</tr>
<tr>
<td>Phenytoin/Fosphenytoin</td>
<td>Class IIb, Level C</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Class IIb, Level C</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Class IIb, Level C</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Class IIb, Level C</td>
</tr>
</tbody>
</table>
Reasons for treatment failure

• Delayed recognition
• Incorrect diagnosis (eg, PNES)
• Anticonvulsivive therapy
  – Poor drug selection
  – Inadequate dosing
  – Failure to continue maintenance AEDs (treatment duration)
• Failure to identify and treat the underlying cause
Summary

**Status epilepticus**: is a life-threatening and not rare condition

- **First**:  
  - to recognize the condition of SE (>5 min seizure state)
- **Second 1**:  
  - to start treatment of SE as much as *early*,  
    because the prognosis of SE worsens with increasing duration  
    → „*time is brain*”
- **Second 2**:  
  - to identify (and treat) the cause (etiology) of SE  
    (*NB: half of the cases of SE *not* due to epilepsy disorder!*)
Magyar Epilepszia Liga
XIII. Kongresszusa

Does Listening to Mozart benefit Children with Severe Epilepsy?
Millichap JG.

Mozart's music in children with epilepsy.
Lin LC, Yang RC.

Exposure to Mozart music reduces cognitive impairment in pilocarpine-induced status epilepticus rats.
Xing Y, Qin Y, Jing W, Zhang Y, Wang Y, Guo D, Xia Y, Yao D.

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Combining non-pharmacological treatments with pharmacotherapies for neurological disorders: a unique interface of the brain, drug-device, and intellectual property.
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Mozart, music and medicine.
Pauwels EK, Volterrani D, Mariani G, Kostkiewics M.

Mozart K.448 listening decreased seizure recurrence and epileptiform discharges in children with first unprovoked seizures: a randomized controlled study.
Lin LC, Lee MW, Wei RC, Mok HK, Yang RC.

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Lin LC, Chiang CT, Lee MW, Mok HK, Yang YH, Wu HC, Tsai CL, Yang RC.