Status epilepticus - state of the art in diagnostic and therapeutic management.

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Systemic effects of SE

Within 30 min SE

- **increased** blood pressure, cardiac output, CBF
- **increased** blood glucose

A **prolonged SE (60min)** leads to **respiratory acidosis**,

- $\text{PaO}_2 \downarrow$ and $\text{PaCO}_2 \uparrow$
- hypoxia and hypercapnia $\Rightarrow$ vasodilatation $\Rightarrow$
- ICP $\uparrow$
- Hypotonia $\Rightarrow$ CPP $\downarrow$
- respiratory/metabolic acidosis
- hyperlactatemia
- hypoglycemia
- hyperglycemia
- hyperpyrexia
Systemic effects of SE

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  - hypoxia and hypercapnia $\rightarrow$ vasodilatation $\rightarrow$
- $\text{ICP} \uparrow$
- $\text{Hypotonia} \rightarrow \text{CPP} \downarrow$
- respiratory/metabolic acidosis $\rightarrow$
- hyperlactatemia
- hypoglycemia
- hyperglycemia
- hyperpyrexia

**blood gas analysis**

**pulse-oximetry is not sufficient**
Definition of SE

Duration of SE

Temporary systemic changes

Life threatening systemic changes

Death

Time point 1 ($t_1$)

“abnormally prolonged seizure”

Start therapy

Time point 2 ($t_2$)

“risk of long-term consequences”

$2^{nd}$-$3^{rd}$ line therapy
Definition of SE

- Treatment should be started
- Status epilepticus should be controlled

**Generalised tonic clonic status epilepticus**

A. 5 min – 30 min

**Focal status with impairment of consciousness**

B. 10 min – 60 min

**Absence status epilepticus**

C. 10 to 15 min

Stage I  Stage II  Stage III

Modified from Trinka & Lowenstein 2015; Epigraph
Pathophysiology ➔ Neuroimaging of SE

Stage 1
- If metabolic demand exceeds hyper-perfusion

Stage 2
- Continuous seizure activity
- High metabolic demand
- $O_2$ and glucose consumption
- Hyperperfusion
- Disruption of the BBB
- Vasogenic edema
- Shift to anaerobic metabolism
- Lactate accumulation
- Failure of Na+/K+ ATPase pump
- Water and Na+ influx

Stage 3
- Cytotoxic edema
- If SE is stopped
- Reversion of neuronal damages
- Irreversible neuronal damages and LT consequences

Stage 4
- If SE is not stopped

Neuroimaging
- Acute stages
  - Differential diagnosis
  - Determine acute consequences (timepoint t2)
- Chronic stage
  - Identify permanent damages of SE

Pathophysiology
- Continuous seizure activity
- High metabolic demand
- $O_2$ and glucose consumption
- Hyperperfusion
- Disruption of the BBB
- Vasogenic edema
- Shift to anaerobic metabolism
- Lactate accumulation
- Failure of Na+/K+ ATPase pump
- Water and Na+ influx
- Cytotoxic edema

Metabolism
- PET
Perfusion
- CTP, SPECT, MRP-ASL
Venous pattern
- SWI
T2/FLAIR, ADC intensity
MRI Contrast Enhancement
- Lac, NAA
  - MRS
DWI, ADC
  - MRI
T2/FLAIR, ADC intensity

Anas et al, Epilepsy Research, 2010; Yu et al, Brain Res Rew, 2008; Cole et al, Epilepsia, 2004; Giovannini and Trinka Epilepsia 2018
Emergency management SE

All patients

❖ Fingerstick **glucose** and **blood gas incl lactate**
❖ **Monitor** vital signs: O2 sat, Temp, BP, HR
❖ Head computed tomography (CT) scan
❖ Order **laboratory** test: blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, **AED levels**.
❖ Continuous electroencephalographic (**EEG**) monitoring if available

➢ IV access → draw blood
➢ administer O2; airway protection
➢ IV glucose?
➢ Thiamin
➢ Benzodiazepines, AED
Handheld Point-of-Care Cerebrospinal Fluid Lactate Testing Predicts Bacterial Meningitis in Uganda

Albert Majwala, Rebecca Burke, William Patterson, Relana Pinkerton, Conrad Muzoora, L. Anthony Wilson, and Christopher C. Moore*

Department of Internal Medicine, Mbarara Regional Referral Hospital, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda; Department of Medicine, Duke University School of Medicine, Durham, North Carolina; Department of Laboratory Medicine, University of Virginia School of Medicine, Charlottesville, Virginia; Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia, Charlottesville, Virginia

\[ R^2 = 0.86, p < 0.001 \]

**Figure 1.** Scatter plot with regression line of average POCL and SLL results (in millimoles per liter) for CSF samples submitted to the clinical laboratory at the University of Virginia.

POCL: point of care lactate
SLL: standard laboratory lactate
Consider the following, based on clinical presentation

- Brain magnetic resonance imaging (MRI)
- Lumbar puncture (LP)
- Comprehensive toxicology panel including toxins that frequently cause seizures (i.e. isoniazid, tricyclic antidepressants, theophylline, cocaine, sympathomimetics, alcohol, organophosphates, and cyclosporine)
- Other laboratory tests: liver function tests, serial troponins, type and hold, coagulation studies, arterial blood gas, AED levels, toxicology screen (urine and blood), and inborn errors of metabolism
SE: Etiology in adults in United States

DeLorenzo et al, Epilepsia ‘92
Convulsive status epilepticus in a quaternary hospital paediatric intensive care unit (PICU) in South Africa: An 8 year review

Yavini Reddy\textsuperscript{a,*}, Yusentha Balakrishna\textsuperscript{b}, Lawrence Mubaiwa\textsuperscript{a}

\textsuperscript{a} Department of Paediatric Neurology, University of KwaZulu-Natal, Durban, South Africa

\textsuperscript{b} Biostatistics Unit, South African Medical Research Council, Durban, South Africa
### Table 2
Aetiology (n = 76).

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>n</th>
<th>[%]</th>
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<tbody>
<tr>
<td>Acute Symptomatic</td>
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<td>(86)</td>
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<tr>
<td>Infections</td>
<td>40</td>
<td>(61)</td>
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<tr>
<td>Gastroenteritis with metabolic derangements</td>
<td>19</td>
<td>(29)</td>
</tr>
<tr>
<td>Trauma related</td>
<td>3</td>
<td>(5 )</td>
</tr>
<tr>
<td>Tumours</td>
<td>2</td>
<td>(3 )</td>
</tr>
<tr>
<td>Intracerebral haematoma</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>Remote Symptomatic</td>
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<td>(8 )</td>
</tr>
<tr>
<td>Idiopathic Epilepsy Related</td>
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<td>(1 )</td>
</tr>
<tr>
<td>Prolonged Febrile</td>
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<td>(4 )</td>
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<tr>
<td>Unclassified</td>
<td>1</td>
<td>(1 )</td>
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### Table 3
Infectious Aetiology Subgroup (n = 40).

<table>
<thead>
<tr>
<th>Infectious Aetiology Subgroup (n = 40)</th>
<th>n</th>
<th>[%]</th>
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</thead>
<tbody>
<tr>
<td>Presumed viral encephalitis</td>
<td>18</td>
<td>(45)</td>
</tr>
<tr>
<td>Bacterial/Viral meningitis</td>
<td>10</td>
<td>(25)</td>
</tr>
<tr>
<td>Tuberculosis meningitis</td>
<td>5</td>
<td>(13)</td>
</tr>
<tr>
<td>Malaria</td>
<td>2</td>
<td>(5 )</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>(10)</td>
</tr>
<tr>
<td>HIV Vasculitis</td>
<td>1</td>
<td>(2 )</td>
</tr>
</tbody>
</table>
### Treatment of SE

#### Stage 1
- **Lorazepam**: 0.05 mg/kg iv, 2 mg/min, max 0.1 mg/kg
- **Diazepam**: 0.15 mg/kg iv, 5 mg/min, max 30 mg
- **Clonazepam**: 0.015 mg/kg iv, 0.5 mg/min, max 3 mg
- **Midazolam**: 0.15 mg/kg, buccal/IN, 0.2 mg/kg
- **Lorazepam**: buccal/IN, 0.2 mg/kg
- **Diazepam**: rektal 10-30 mg

#### Stage 2
- **Phenytoin**: 20 mg/kg, 50-100 mg/min, 5-7 mg/kg/d
- **Valproic acid**: 30 mg/kg, 10 mg/kg/min, 30-60 mg/kg/d
- **Levetiracetam**: 50-100 mg/kg, 100 mg/min, 2-12 g/d
- **Lacosamide**: 5 mg/kg, within 15 min, 400-600 mg/d
- **Phenobarbital**: 20 mg/kg, 100 mg/min, 1-4 mg/kg/d

#### Stage 3
- **Midazolam**: 0.2 mg/kg load, 0.1-0.4 mg/kg/h
- **Propofol**: 2-3 mg/kg load, 5-10 mg/kg/h
- **Thiopental**: 5 mg/kg load, 3-7 mg/kg/h

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1. **Intubation** should be done after the administration of a barbiturate bolus of 3-5 mg/KG bw (e.g. Thiopental). This dosage usually allows sufficient “relaxation” to facilitate the placement of the endotracheal tube.

2. Neuromuscular blockade should not be given in these patients, however, if absolutely necessary, Vecuronium 0,1 mg/kg bw. can be considered.

3. Monitor body temperature, **maintain normothermia**.

4. Pentobarbital 5-15 mg/KG bw. over 1 h (or **Thiopental** 3-7 mg/kg bw/h), then continue Pentobarbital 0,5-5 mg/KG/bw/h (or continue **Thiopental** at a rate of 1-3 mg/kg bw/h) until seizures are controlled.

5. **Monitor** with **continuous** EEG
6. Intra-arterial line for **blood gas analysis**, invasive **blood pressure monitoring**

7. Invasive **hemodynamic monitoring**, e.g. PiCCO or even more invasive monitoring.

8. Titrate the dosage of barbiturates against **EEG burst suppression** pattern.
**Burst suppression EEG**

- **burst-suppression-EEG for at least 24 hours**

  **Endpoints** remain *controversial* and options include:
  - burst suppression
  - complete background suppression
  - seizure suppression

**Withdrawal seizures:**

- restart *MDZ* or change to different clV-AED
- maximize other *AEDs* or add AED
- **Taper again** after no seizures for 24-72 hrs

*Bauerschmidt et al, Curr Opin Crit Care 2017, 23:122–127*
6. Intra-arterial line for **blood gas analysis, invasive blood pressure monitoring**

7. Invasive **hemodynamic monitoring**, e.g. PiCCO or even more invasive monitoring.

8. Titrate the dosage of barbiturates against **EEG burst suppression pattern**.

9. **Fluid management, aggressive fluid balancing**, if necessary **catecholamines**

10. **Monitoring** must be on high alert to recognize any **incipient nosocomial infection** (regular culturing of body fluids, regular C-reactive protein, procalitonin, WBC, etc.).
Receptor trafficking in prolonged seizure activity

Pathologic Mechanism

- Inhibition Failure: GABA-Responsive
- Excess Excitation: GABA-Unresponsive

Pathophysiology

- Receptor Trafficking: ↓GABA (endocytosis)  ↑NMDA upregulation
- Rapid Synaptic Plasticity: GABA Receptor composition changes
- Altered Gene Expression:
  - Multi-Drug Efflux Transporters (i.e. P-Glycoprotein)
  - Drug Resistance Proteins
  - Drug Target Alterations

Systemic Pathology

- Sympathetic Overdrive
- Homeostatic Failure

Clinical Stages

- Acute Sz
- Early or Impending Status
- Established SE
- Refractory SE
- Malignant SE
- Superrefractory SE

Mortality

- <1%
- <5%
- <20%
- 30%
- 40%
- 60%

< 2 min 10 min 30 min 1 hr 6 hr 10 hr Days

Grover et al, Curr Treat Options Neurol (2016) 18: 11
New AED in therapy refractory SE

Ketamine
Bolus: 0.5–4.5 mg/kg
M: up to 7.5 mg/kg/h

- NMDA antagonist

- **Neuroprotective**
  - mechanism backed by animal data esp for prolonged SE
  - Barbiturates and benzos *work well early* in SE, not late
  - Ketamine is opposite, *in SE >1h (=late)* (expert opinion)

*Borris 2000; Mazarati 1998, 1999*

- **Less hemodynamic side effects** (compared to Barbiturates and Propofol)
**Definition SRSE**

1. **Stage 1: First 30 minutes**
   - **Early Status Epilepticus**
   - Treat with benzodiazepines - for instance IV lorazepam, buccal midazolam, IV or rectal diazepam

2. **Stage 2: 30-120 minutes**
   - **Established Status Epilepticus**
   - Treat with IV antiepileptic drugs – for instance, phenytoin, phenobarbital or valproate

3. **Stage 3: >120 minutes**
   - **Refractory Status Epilepticus**
   - Treat with general anaesthesia – for instance, propofol, midazolam, or thiopental/pentobarbital

**After 24 hours**

**Super-refractory Status Epilepticus:** Status epilepticus which has continued or recurred despite therapy with general anaesthesia for 24 hours or more

*Shorvon S, and Ferlisi M* Brain 2011;134:2802-2818
**Therapeutic options in SRSE**

**Table 1** The evidence base for treatments used in super-refractory status epilepticus

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Published cases in controlled or randomized studies (n)</th>
<th>Published cases in open series or as case reports (reports, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentobarbital/thiopental</td>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>377 (32)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0</td>
<td>661 (29)</td>
</tr>
<tr>
<td>Propofol</td>
<td>14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>183 (34)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Inhalational anaesthetics</td>
<td>0</td>
<td>32 (11)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>0</td>
<td>10&lt;sup&gt;c&lt;/sup&gt; (5)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Pyrroline</td>
<td>0</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Steroids/immunotherapy</td>
<td>0</td>
<td>50 (15)</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>0</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Transcranial magnetic stimulation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vagal nerve stimulation</td>
<td>0</td>
<td>4 (4)</td>
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<tr>
<td>Deep brain stimulation</td>
<td>0</td>
<td>1&lt;sup&gt;b&lt;/sup&gt; (1)</td>
</tr>
<tr>
<td>Resective neurosurgery</td>
<td>0</td>
<td>36 (15)</td>
</tr>
<tr>
<td>CSF drainage</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Electroconvulsive therapy</td>
<td>0</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

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**Immunotherapy:**
- 1000mg methylprednisolone for 3d followed by 1mg/kg/day for 1 week
  - 30g IV Immunoglobulin for 3 to 5d
  - 3 to 5 cycles Plasma exchange

**Hypothermia:** 32-35°C < 48h (neg. RCT!)

**Ketogenic diet:** (1:1 to 1:4)

ECT, CSF-drainage, withdrawal of AEDs and others

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*Shorvon S, and Ferlisi M* Brain 2011;134:2802-2818

*Trinka et al* DRUGS 2015
Periodic discharge >2Hz associated with **brain tissue hypoxia**

*Witch et al, JAMA Neurol. 2017 Mar 1;74(3):301-309*

Epileptiform activity associated with **metabolic distress**
(decreased CMD-glucose and increased CMD-LPR)

*Vespa et al, Ann Neurol 2016;79:579–590*
Guidelines for the Evaluation and Management of Status Epilepticus

Gretchen M. Brophy · Rodney Bell · Jan Claassen · Brian Alldredge · Thomas P. Bleck · Tracy Glauser · Suzette M. LaRoche · James J. Riviello Jr. · Lori Shutter · Michael R. Sperling · David M. Treiman · Paul M. Vespa · Neurocritical Care Society Status Epilepticus Guideline Writing Committee

### Outcome SE, NCSE, RSE

<table>
<thead>
<tr>
<th></th>
<th>GCSE</th>
<th>NCSE</th>
<th>RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>9-21%</td>
<td>18-52%</td>
<td>23-62%</td>
</tr>
<tr>
<td>At 30d</td>
<td>19-27%</td>
<td>65%</td>
<td>39%</td>
</tr>
<tr>
<td>At 90d</td>
<td>19%</td>
<td></td>
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</table>
Summary

❖ SE is an emergency and warrants immediate aggressive treatment

❖ RSE, SRSE are still associated with high morbidity and mortality

❖ Unclear how much additional damage caused by seizures but suggestive that seizures are not good for the acutely injured brain

❖ Neurotoxicity of SE

❖ Often will need cEEG monitoring for SE in ICU → call for multimodal neuromonitoring

❖ Many treatment options