CRITICAL CARE MANAGEMENT OF STATUS EPILEPTICUS

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OBJECTIVES

• Review the latest guideline from the American Epilepsy Society on the treatment of status epilepticus.
• Discuss an algorithm for management.
• Explore novel approaches to SE treatment
DEFINITION

- **Status epilepticus (SE)**
  - A seizure that lasts longer than 5 minutes or two or more seizures without return to baseline

- **Refractory status epilepticus (RSE)**
  - Ongoing seizure despite treatment with a benzodiazepine and antiepileptic drug (AED)

- **Super-refractory status epilepticus (SRSE)**
  - Continuous or recurrent seizure lasting 24 hrs. or more following initiation of anesthetic medications, or recurrent seizure after weaning off the anesthetic agent
INTRODUCTION

• Medical Emergency
• Incidence of 60 cases per 100,000
• Mortality rate of 7 – 28%
  • Age
  • Medical comorbidities
  • Presence of nonconvulsive status epilepticus (NCSE)
  • Underlying cause
CAUSES

- Genetic influence
- Head trauma
- Brain conditions
- Infectious diseases
- Prenatal injury
- Developmental disorders
The new definition and classification of seizures and epilepsy

Jessica J. Falco-Walter a_GB, Ingrid E. Scheffer b_GB, Robert S. Fisher a_GB

• Based on 3 key features
  ✓ Onset location
  ✓ Level of awareness
  ✓ Other features
    ➢ Motor
    ➢ Auras
ONSET LOCATION

- **Focal seizure**
  - ✓ Previously called partial seizure
  - ✓ Begin in an area or network of cells on one side of the brain
- **Generalized seizure**
  - ✓ Networks of cells on both sides of the brain
- **Unknown onset seizure**
- **Focal to bilateral seizure**
  - ✓ Starts on one side and spreads to both sides
LEVEL OF AWARENESS

• Focal aware  
  ✓ Person remains aware, even if unable to speak or respond

• Focal impaired awareness  
  ✓ Complex partial seizure  
  ✓ Awareness is impaired or affected  
  ✓ Person may have a vague idea

• Awareness unknown

• Generalized seizure

Falco-Walter, JJ, et al., Epilepsy Research 2017
MOTOR SYMPTOMS

• Focal motor seizure
  ✓ Some type of movement occurs
  ✓ Twitching
  ✓ Jerking
  ✓ Stiffening of a body part
  ✓ Automatisms

• Focal non-motor seizure
  ✓ Changes in sensation
  ✓ Emotions
  ✓ Thinking
  ✓ Experiences

• Generalized motor seizure
  ✓ Generalized tonic-clonic
  ✓ Grand mal
  ✓ Stiffening (tonic) and jerking (clonic)

• Generalized non-motor seizure
  ✓ Absence
  ✓ Petit mal
  ✓ Brief changes in awareness, staring
  ✓ Automatic or repeated movements
# ILAE 2017 Classification of Seizure Types Expanded Version

## Focal Onset

<table>
<thead>
<tr>
<th>Aware</th>
<th>Impaired Awareness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Onset</strong></td>
<td></td>
</tr>
<tr>
<td>automatisms</td>
<td>atonic&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>clonic</td>
</tr>
<tr>
<td></td>
<td>epileptic spasms&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>hyperkinetic</td>
</tr>
<tr>
<td></td>
<td>myoclonic</td>
</tr>
<tr>
<td></td>
<td>tonic</td>
</tr>
<tr>
<td><strong>Non-Motor Onset</strong></td>
<td></td>
</tr>
<tr>
<td>autonomic</td>
<td>behavior arrest</td>
</tr>
<tr>
<td></td>
<td>cognitive</td>
</tr>
<tr>
<td></td>
<td>emotional</td>
</tr>
<tr>
<td></td>
<td>sensory</td>
</tr>
</tbody>
</table>

- focal to bilateral tonic-clonic

## Generalized Onset

<table>
<thead>
<tr>
<th><strong>Motor</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>tonic-clonic</td>
</tr>
<tr>
<td>clonic</td>
</tr>
<tr>
<td>tonic</td>
</tr>
<tr>
<td>myoclonic</td>
</tr>
<tr>
<td>myoclonic-tonic-clonic</td>
</tr>
<tr>
<td>myoclonic-atonic</td>
</tr>
<tr>
<td>atonic</td>
</tr>
<tr>
<td>epileptic spasms</td>
</tr>
</tbody>
</table>

- Non-Motor (absence)
  - typical |
  - atypical |
  - myoclonic |
  - eyelid myoclonia |

## Unknown Onset

<table>
<thead>
<tr>
<th><strong>Motor</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>tonic-clonic</td>
</tr>
<tr>
<td>epileptic spasms</td>
</tr>
</tbody>
</table>

- Non-Motor |
  - behavior arrest |

- **Unclassified**

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<sup>1</sup> Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

<sup>2</sup> Degree of awareness usually is not specified

<sup>3</sup> Due to inadequate information or inability to place in other categories
MANAGEMENT

• Neurologic life support
• Peripheral intravenous access
• Medications
• Workup
## AES ALGORITHM

**Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics**

1. **Stabilize patient** (airway, breathing, circulation, disability - neurologic exam)
2. **Time seizure from its onset, monitor vital signs**
3. **Assess oxygenation; give oxygen via nasal cannula/mask; consider intubation if respiratory assistance needed**
4. **Initiate EEG monitoring**
5. **Collect finger stick blood glucose. If glucose < 60 mg/dl then**
   - Adults: 100 mg thiamine IV then 50 ml D50W IV
   - Children ≥ 2 years: 2 ml/kg D25W IV
   - Children < 2 years: 4 ml/kg D12.5W
6. **Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels**

### 0-5 min Stabilization phase

| 0-5 min Stabilization phase | Does Seizure continue?
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### 5-20 min Initial therapy phase

If patient at baseline, then symptomatic medical care.

**A benzodiazepine is the initial therapy of choice (Level A):**

Choose one of the following 3 equivalent first-line options with dosing and frequency:

- Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR
- Intravenous lorazepam (0.1-0.2 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
- Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)

If none of the 3 options above are available, choose one of the following:

- Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
- Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
- Intrasanasal midazolam (Level B), buccal midazolam (Level B)

### 20-40 min Second therapy phase

If patient at baseline, then symptomatic medical care.

**There is no evidence based preferred second therapy of choice (Level U):**

Choose one of the following second-line options and give as a single dose:

- Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose, Level U) OR
- Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
- Intravenous levetiracetam (400 mg/kg, max: 4500 mg/dose, single dose, Level U)

If none of the options above are available, choose one of the following (if not given already):

- Intravenous phenobarbital (15 mg/kg, max dose, Level B)

### 40-60 min Third therapy phase

If patient at baseline, then symptomatic medical care.

**There is no clear evidence to guide therapy in this phase (Level U):**

Choices include: repeat second-line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).
SHEN’S ALGORITHM

0 – 5 min
• Stabilization
• Labs, IV

5 – 15 min
• Initial Therapy
• Benzodiazepine x 1-2
• AED

15 – 30 min
• Intubation
• Propofol bolus -> gtt
• AED
THERAPY

• Initial Emergent Therapy
  ✅ Benzodiazepines
• Second Urgent-control Therapy
  ✅ Antiepileptic drug (AED)
• Third Refractory Therapy
INITIAL EMERGENT THERAPY

• Benzodiazepines
  ✓ Lorazepam
  ✓ Midazolam
  ✓ Diazepam
  ✓ Clonazepam
SECOND URGENT-CONTROL THERAPY

- Antiepileptic drug (AED)
  - ✔ Phenytoin/fosphenytoin
  - ✔ Valproic acid
  - ✔ Levetiracetam (Keppra)
  - ✔ Lacosamide (Vimpat)
  - ✔ Phenobarbitol
  - ✔ Carbamezepine (Tegretol)
THIRD REFRACTORY THERAPY

• Aggressive phase
• Continuous EEG
• Repeat second-line therapy
• Anesthetic dose
  ✓ Thiopental
  ✓ Midazolam
  ✓ Pentobarbital
  ✓ Propofol
BENZODIAZEPINES

• GABA receptor agonist
• Routes of administration
  ✓ Intravenous
  ✓ Nasal
  ✓ Buccal
  ✓ Rectal
• Respiratory depression
DIAZEPAM

• Higher brain concentration
• Onset of action 30 seconds
• Highly lipid soluble
• Rapid redistribution and decreased brain concentration
• Clinical effectiveness about 20 minutes
MIDAZOLAM

• Any route of administration
• Intramuscular, rectal, sublingual, intranasal
• Half life 1.5 to 2.5 hrs.
LORAZEPAM

• Onset of action 2 minutes
• Duration of action greater than 12 hrs.
WHY USE BENZO FIRST?

A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus

• 5 year randomized, double blind
• 570 patients
• 16 Veterans Affairs medical centers and 6 affiliated university hospitals

Treiman DM, et al., JAMA 1998
A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus

**Treatment regimen**

 ✓ phenobarbital (15mg/kg)
 ✓ phenytoin (18mg/kg)
 ✓ diazepam (0.15mg/kg) plus phenytoin (18mg/kg)
 ✓ lorazepam (0.1mg/kg)
A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus

• Treatment success
  ✓ Seizure cessation within 20 min
  ✓ No return of seizure activity for 40 min

- Randomized, double-blind trial
- Intravenous benzodiazepines
- Prolonged seizure (> 5 min)
- Repetitive generalized convulsive seizure

• 205 patients
  ✓ 66 received 2mg lorazepam
  ✓ 68 received 5mg diazepam
  ✓ 71 received placebo

**Table 2. Status Epilepticus at the Time of Arrival at the Emergency Department.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lorazepam Group (N = 66)</th>
<th>Diazepam Group (N = 66)</th>
<th>Placebo Group (N = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status epilepticus terminated</td>
<td>39 (59.1)</td>
<td>29 (42.6)</td>
<td>15 (21.1)</td>
</tr>
<tr>
<td>Ongoing status epilepticus</td>
<td>27 (40.9)</td>
<td>39 (57.4)</td>
<td>56 (78.9)</td>
</tr>
</tbody>
</table>

Odds ratio (simultaneous 95 percent CI) for termination of status epilepticus

- Unadjusted: 5.4 (2.3–13.2), 1.9 (0.9–4.3), 2.8 (1.2–6.7)
- Adjusted: 4.8 (1.9–13.0), 1.9 (0.8–4.4), 2.3 (1.0–5.9)

*CI denotes confidence interval.
† Each odds ratio was adjusted for race or ethnic group, the intervals from the onset of status epilepticus to study treatment and from study treatment to arrival at the emergency department, and cause of status epilepticus within each prognostic group.

• Benzodiazepines are safe and effective
Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis.

- 6 studies
- 774 subjects
- Midazolam by any route was superior to diazepam
• 4314 paramedics
• 33 EMS agencies
• 79 receiving hospitals
• Double-blind, randomized, noninferiority trial
• 893 patients
• Intramuscular midazolam 10mg
• Intravenous lorazepam 4mg

• Result: Absent seizure without rescue therapy at ED arrival
  ✓ IM midazolam 73.4%
  ✓ IV lorazepam 63.4%
SHEN’S ALGORITHM

0 – 5 min
• Stabilization
• Labs, IV

5 – 15 min
• Initial Therapy
• Benzodiazepine x 1-2
• AED

15 – 30 min
• Intubation
• Propofol bolus -> gtt
• AED
SECOND URGENT CONTROL THERAPY

• The Antiepileptic drugs (AED)
• No strong data supporting the use of one over another
• Use is dependent on availability, preference, side effect profile
• Emergent therapy fails to control 35 – 45% of patients
AEDs: Mechanisms of Action

Voltage-gated sodium channel

Open

\[ \text{Na}^+ \]

Inactivated

\[ \text{Na}^+ \]

Carbamazepine
Phenytoin

Lamotrigine
Valproate
AEDs: Mechanisms of Action

- **Calcium channel blockade**

  Calcium channel blocker prevents release of internal calcium stores into cell cytosol.

  Cell does not respond to calcium ion signal.
AEDs: Mechanisms of Action

- GABA

GABA elevates GABA levels by irreversibly inhibiting its main catabolic enzyme, GABA-transaminase.

Vigabatrin interfere with GABA reuptake.

Tiagabine

Succinic semi-aldehyde

GABA-T

GABA

Glutamate

GAD

Inhibitory presynaptic terminal

GABA

Felbamate, topiramate, zonisamide

Benzodiazepines

Barbiturates

Postsynaptic neuron

GABA_a receptor

Cl^-

GAT1
PHENYTOIN

• Decreases the recovery rate of voltage-activated sodium channel
• pKa 8.3, highly lipid soluble but insoluble in water
• Highly protein bound, one free portion is active
• Mixed in polypropylene glycol pH 12
• Metabolized by liver, has saturable pharmacokinetics
• Slow infusion rate 50mg/min
• Delayed onset of action
• Complications include hypotension and cardiac arrhythmia
• If extravasation occurs, causes local irritation, thrombophlebitis, compartment syndrome, “purple glove syndrome”
FOSPHENYTOIN

• Water-soluble precursor which is rapidly transformed to phenytoin
• Faster rate of infusion 150mg/min, can also be given IM
• Higher cost
VALPROIC ACID

- Is most prescribed AED worldwide
- Maximum plasma concentration reached within minutes
- Highly protein bound to plasma protein (>90%)
- Metabolized extensively in liver
- Half-life 12 h
- Non-sedating, No cardiac toxicity
- Low adverse event rate (<10%) dizziness, thrombocytopenia, mild hypotension, pancreatitis, hyperammonia
LEVETIRACETAM

• Minimal hepatic metabolism and low plasma protein binding
• Excreted renally and needs to be adjusted for renal failure
• Low rate of adverse effects
  ✓ Somnolence and sedation
  ✓ Agitation
  ✓ Thrombocytopenia

Misra UK, et al., J Neural 2012
LACOSAMIDE

• Acts as a sodium channel blocker, by enhancing slow inactivation
• Slightly bound to plasma protein (<15%)
• 95% is excreted in the urine, 30% as inactive metabolite
Single tertiary care hospital
187 patients
Treatment with intravenous benzodiazepines followed by:
- ✓ Phenytoin 20 mg/kg
- ✓ Valproate 20 mg/kg
- ✓ Levetiracetam 20 mg/kg

✓ Valproate was most effective
The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies

- 27 studies
- Mean efficacy termination of seizure within 30 min
  - valproate 75.7%
  - phenobarbital 73.6%
  - levetiracetam 68.5%
  - phenytoin 50.2%
- Lacosamide was excluded due to insufficient data
REFRACTORY THERAPY

• Anesthetic
  ✓ Propofol
  ✓ Midazolam
  ✓ Thiopental
  ✓ Pentobarbital
• Ketamine
• Ketogenic diet
• Immunologic therapy
• Electroconvulsive therapy (ECT)
• Surgery
PROPOFOL

• Potentiation of GABA receptor binding
• NMDA antagonism
• Lipid-soluble emulsion that results in rapid onset and offset
• Hypotension and bradycardia
• Propofol infusion syndrome (PRIS)
MIDAZOLAM

• Used to induce coma
• Lacks propylene glycol diluent
• Hepatic metabolism, active metabolite is renally eliminated
PENTOBARBITAL

• Long acting barbiturate
• Causes significant cardiovascular and respiratory depression and hypotension
• Needs vasopressor support
• Half-life of 15-48 hrs, but may take days to weeks for complete elimination
KETAMINE

• NMDA receptor antagonist
• Stable hemodynamic profile
• Potential for increasing intracranial pressure
Ketamine use in the treatment of refractory status epileptics.

Synowiec AS¹, Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM.

- Retrospective review
- 11 patients
- Dose 0.45 to 2.1 mg/kg/h
Ketamine use in the treatment of refractory status epilepticus.

Synowiec AS¹, Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM.

• Adverse reactions
  ✓ Psychiatric symptoms
  ✓ Increased ICP
  ✓ Increased secretion of saliva
  ✓ Increased intraocular pressure
  ✓ Arrhythmia
  ✓ Neurotoxicity
ALTERNATIVE THERAPY

- Therapeutic hypothermia
- Immunomodulatory therapy
- Deep brain stimulation
- Ketogenic diet
- Surgery
- Electroconvulsive therapy
- Vagal nerve stimulation
• 11 French ICU
• 270 patients
• Treatment:
  ✓ 32 to 34°C for 24 hours in addition to standard care
  ✓ standard care
• Functional Outcome at 90 days
  ✓ Glasgow Outcome Scale (GOS) of 5
• Hypothermia group 49%
• Control group 43%
Hypothermia for Neuroprotection in Convulsive Status Epilepticus

Stephane Legriel, M.D., Virginie Lemiale, M.D., Maleka Schenck, M.D., Jonathan Chelly, M.D., et al., for the HYBERNATUS Study Group*
• Neurosteroid allopregnanolone
  • Metabolite of progesterone
• Acts as a positive modulator of synaptic and extrasynaptic GABA$_A$ receptors
Pediatric super-refractory status epilepticus treated with allopregnanolone.

Broomall E¹, Natale JE, Grimason M, Goldstein J, Smith CM, Chang C, Kanes S, Rogawski MA, Wainwright MS.

• Patient 1
• Reading
• Learning to play the piano
• Patient 2
• HD 15
• Meeting milestones

• No adverse effects of treatment
• Allowed withdrawal of all general anesthetic infusions
• 17 y.o. not resolved with propofol, thiopental, midazolam, or ketamine coadministered with multiple AEDs and IVig
• Centromedian nucleus of thalamus
• 4.5 month old boy with right hemispheric cortical dysplasia
• Right hemispherotomy was done after 10 days
• 7 y.o. boy with 3 yr. history of right-sided focal motor seizure
• Progressive left cerebral atrophy
• Hemispherotomy done after 7 days
• 24 yr. old man presented with delirium and shouting of meaningless words, 2 days after fever related to URI
• Pt developed clonic seizure on left side of his face that sometimes evolved into generalized tonic-clonic seizure
• At 14 months, pt. was bedridden, unable to communicate verbally, required a PEG, on IV midazolam
• 1 yr. seizure free after VNS
REFERENCES

- Epilepsy Curr. 2016 16(1); 48-61 Evidence-Based Guideline; Treatment of Convulsive Status Epilepticus in Children and Adults; Report of the Guideline Committee of the American Epilepsy Society.


