Treatment of Status Epilepticus in Adults

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Disclosures

• Demos Publishing- royalties

• Member of the Neurocritical Care Society SE guidelines committee, 2012
Outline

• Definitions

• Etiologies

• Treatment

• Questions That Remain
What is Status Epilepticus?

1867: Trousseau
   “When the convulsive condition is almost continuous, something special takes place which requires an explanation.”

1962: Gastaut
   “A seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition”

1993: American Epilepsy Society Operational Definition
   30 min of continuous seizure activity or recurrent seizures without recovery of consciousness

1998: VA SE Cooperative Trial
   10 min of continuous seizure activity

1999: Revised Operational Definition
   5 min of continuous seizure activity or 2 or more seizures without return to baseline
ILAE 2015

• “A condition that leads to abnormally prolonged seizures (Time point 1) and can have long term consequences (Time point 2)”

• GTC seizures (animal data)
  – Time Point 1= 5 minutes,
  – Time Point 2= 30 minutes

• Other seizure types- Not great models

Trinka et al, Epilepsia, 2015

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ILAE, 2015

• Diagnostic Classification System
  – Axis I    Semiology
  – Axis II   Etiology
  – Axis III  EEG Correlate
  – Axis IV   Age

Trinka et al, Epilepsia 2015

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Generalized Convulsive Status Epilepticus (GCSE)

- Initial presentation in 7% of all epilepsy cases (higher in infants and elderly)

- Common causes: Noncompliance, Stroke, Anoxia

- Mortality up to 50%, determined primarily by etiology

- Poor predictors: older age, SE>1 hour, Anoxic injury
Non-Convulsive Status Epilepticus (NCSE)

- Generalized
  - No overt motor manifestations
  - Coma
  - Generalized spikes, spike wave

- Complex Partial
  - Impaired consciousness
  - May have episodic motor manifestations-automatisms, focal clonic activity, dystonic posturing
    - Focal/hemispheric rhythmic theta, delta

- Absence (spike-wave stupor)
  - 3 Hz generalized spike wave
EEG Definition of NCSE
“Salzburg Criteria”

At least 10 second duration and one of the following:

1. Epileptic discharges > 2.5 Hz
2. Spatiotemporal evolution of EDs or rhythmic delta activity (> 0.5 Hz)
3. Subtle ictal clinical phenomena

Possible NCSE: Criteria 1–3 are not fulfilled, but one of the following is present:

1. EDs ≤ 2.5 Hz with fluctuation
2. Rhythmic delta activity > 0.5 Hz with or without fluctuation

Beniczky et al, Epilepsia 2013
Refractory Status Epilepticus (RSE)

• RSE Definition
  – Ongoing seizures despite 2 appropriate AEDs including a benzodiazepine

• Super RSE (SRSE)
  – Introduced at London-Innsbrook SE Colloquium 2011
  – Continuous or recurrent seizures >24 hrs requiring anesthetic agents

• Often absence of motor movements at this stage, hence an EEG diagnosis

Novy Epilepsia 2010, Shorvon Epilepsia 2011
Uncommon Causes of SE/RSE

- Limbic Encephalitis
  - Paraneoplastic (small cell, testicular, breast)
  - Non-paraneoplastic (VGKC complex/LGI1, GAD)
  - NMDA receptor Ab (+/- ovarian teratoma)
- Other Autoimmune encephalitis
  - Hashimoto’s thyroiditis, SLE, Wegener’s
- Infectious
  - Bartonella, Syphillis, Coxiella, Mycoplasma
  - HIV, JC virus, Varicella, SSPE, Parvo, Arboviruses, Polio
  - Coccidiomycosis, Mucormycosis, Aspergillosis, Candidiasis
  - Cretuzfeldt-Jacob disease
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Subacute encephalopathy and seizures in alcoholics (SESA)
- Neoplastic
New Onset Refractory Status Epilepticus (NORSE)

• First defined by Wilder-Smith et al 2005
• Highly refractory SE in previously healthy adults
• No clear immediate cause
  – CSF pleocytosis common, presumed “viral”
  – Imaging abnormalities often nonspecific
    • T2/Flair/DWI changes in cortical ribbon
    • High T2/Flair in mesial temporal lobes (limbic)
  – Cause or effect of seizures
NORSE Retrospective Study
84 patients, 11 sites

Autoimmune (31):
- anti-NMDAR: 11
- Anti-VGKCC: 5
- Anti-GAD: 2
- Neurolupus: 2
- SREAT: 2
- Seronegative: 4
- Others: 5
- Paraneoplastic: 18
- Non-paraneoplastic: 12

Infectious (7):
- WNV: 2
- CMV: 1
- EBV: 1
- Neurosyphilis: 1
- T. gondii: 1
- M. pneumoniae: 1

Others (4):
- Carcinomatosis: 2
- SESA: 2

NORSE (42)

Gaspard et al Neurology, 2015

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Lorazepam vs. Diazepam*

Leppik, I. JAMA; 1983, 249: 1452-4
RAMPART: Rapid Anticonvulsant Medication Prior to Arrival Trial

- IV lorazepam vs. IM midazolam for seizures > 5 min
- 900 patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Time to Rx</th>
<th>Time to cessation</th>
<th>Sf Free*</th>
<th>Intubated</th>
</tr>
</thead>
<tbody>
<tr>
<td>LZP</td>
<td>4 mg</td>
<td>4.8 min</td>
<td>6.4 min</td>
<td>63.4%</td>
<td>14.4%</td>
</tr>
<tr>
<td>MDZ</td>
<td>10 mg</td>
<td>1.2 min</td>
<td>4.5 min</td>
<td>73.4%</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

* Non-inferiority and Non-superiority p<0.001, CI 4.0 to 16.1

Silbergleit, NEJM, 2012
Initial Treatment of GCSE (VA Coop Trial)

LZP superior to PHT

VPA vs. PHT (Class III RCTs)

- 68 pts. GCSE, VPA (30 mg/kg) vs. PHT (18 mg/kg)
  - Efficacy as 1\textsuperscript{st} line: VPA 66%, PHT 42%
  - Efficacy as 2\textsuperscript{nd} line: VPA 79%, PHT 25%

- 74 pts. “Clinical SE”, VPA (30mg/kg) vs PHT (18 mg/kg)
  - VPA 87.8% vs. PHT 88% seizure free
  - PHT 12% side effects, VPA none

- Disadvantages
  - Hepatotoxicity, Pancreatitis, Thrombocytopenia, Encephalopathy

Initial Treatment for RSE

Midazolam 0.2 mg/kg slow IV bolus;
  maintenance of 0.1-2 mg/kg/hr
Propofol 3-5 mg/kg IV bolus;
  maintenance 1-15mg/kg/hr
Pentobarb 5-15 mg/kg IV bolus;
  maintenance of 1-10 mg/kg/hr
  OR
Phenobarbital load 20 mg/kg, 50-100 mg/min
Valproate IV load 30-40 mg/kg, 3-5 mg/kg/min
Treatment of Refractory SE: a literature review


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Other Options

• Levetiracetam
  – Up to 60 mg/kg load, max 4500 mg IV
  – Open Label, 79 pts: LEV (20 mg/kg) vs. LZP (0.1 mg/kg)
    • LEV: 76.3% vs. LZP 75.6% seizure free at 10 min
    • Cross over- LEV 70% vs. LZP 88.9%
    • LZP Increased hypotension and intubation

• Lacosamide
  – Load 200-400 mg IV, then 200 mg q12 hours
  – Treatment of Recurrent Electrographic Non-convulsive seizures (TRENdS)
    • LCM (400 mg) vs. fPHT (20 mg/kg) for recurrent seizures, 62 pts
    • Seizure free at 24 hrs: LCM 63.3% vs fPHT 50%
    • Non-inferior, and AEs similar

Misra et al, J Neurol 2012
Husain et al, AES 2015
Evidence Based Guidelines

• Neurocritical Care Society, 2012
  – Broader scope: Diagnosis, Non-Pharmacological management
  – ICU focused, incudes NCSE
  – AHA rating system

• American Epilepsy Society, 2016
  – GSCE only
  – Emphasis on 1\textsuperscript{st}, 2\textsuperscript{nd} line
  – AAN rating system

# Rating Systems

## AHA

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class I: Benefits &gt;&gt; Risk, should be used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Class IIa: Benefits &gt; Risk, reasonable</td>
</tr>
<tr>
<td></td>
<td>Class IIb: More data needed, may consider</td>
</tr>
<tr>
<td></td>
<td>Class III: No benefit, may be harmful</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>A</th>
<th>Multiple large RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Single RCT, non-RCTs, observational</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Expert opinion, case reports</td>
</tr>
</tbody>
</table>

## AAN

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level A: Established, should be used</th>
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<tbody>
<tr>
<td></td>
<td>Level B: Probably, should be considered</td>
</tr>
<tr>
<td></td>
<td>Level C: Possibly, may consider</td>
</tr>
<tr>
<td></td>
<td>Level U: Insufficient data, no recc</td>
</tr>
</tbody>
</table>

| Level of Evidence (All RCTs) | A  | 1 or more class I, 2 or more class II |
|                             | B  | 1 or more class II, 3 or more class III |
|                             | C  | 2 or more class III                   |
|                             | U  | Lack of studies                       |
First Line

**NCS** (Emergent)
- Lorazepam, Midazolam
  - Definitely, Level A
- Diazepam
  - Probably, Level A
- PHT, PB, VPA
  - Maybe, Level A
- LEV
  - Maybe, Level C

**AES** (5-20 min)
- IV Lorazepam, IM Midazolam, IV diazepam
  - Definitely, Level A
- If above not feasible
  - IV Phenobarbital, Level A
  - Rectal diazepam, Level B
  - IN midazolam, Level B

Brophy et al, J NeuroCrit Care 2012  
Glauser et al, Epil Curr 2016
Second Line

**NCS** (Urgent)
- Valproate
  - Probably, Level A
- fPHT/PHT
  - Probably, Level B
- Midazolam
  - Maybe, Level B
- Phenobarbital, LEV
  - Maybe, Level C

**AES** (20-40 min)
- Valproate
  - Probably, Level B
- fPHT, LEV
  - Level U
- Phenobarbital
  - If no other options available, Level B

* Level U- No evidence any agent is better

Brophy et al, J NeuroCrit Care 2012  
Glauser et al, Epil Curr 2016

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Refractory

**NCS**
- Midazolam, Valproate
  - Probably, Level B
- Propofol, Pentobarb
  - Maybe, Level B
- Phenobarb, LEV, TPX, LCM, PHT
  - Maybe, Level C

**AES (40-60 min)**
- All Level U
- Repeat second line therapy
- Thiopental, midazolam, pentobarbital, propofol

Brophy et al, J NeuroCrit Care 2012  
Glauser et al, Epil Curr 2016
Need Better Data!!!

- Established SE Treatment Trial (ESETT)
- Randomized Control Trial for Benzo refractory SE
  - fPHT 20 mg/kg (20 min)
  - Valproic acid 30 mg/kg (10 min)
  - Levetiracetam 60 mg/kg (10 min)

- 800 patients, 3 age groups (> 2 years), 40 sites
- Primary Outcome
  - Cessation of CLINICAL seizures and improved mental status at 60 min
  - With no further intervention or serious SE

NCSE excluded
EEG Monitoring NOT Included
Funding not finalized, under review by NIH

Bleck, Epilepsia 2013
Is It Time To Get Rid of Timelines?

<table>
<thead>
<tr>
<th>Time</th>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>Stage I-early SE</td>
<td>IV benzodiazepines-lorazepam, midazolam, diazepam</td>
</tr>
<tr>
<td>30-120 min</td>
<td>Stage II-established SE</td>
<td>IV phenobarbitone, phenytoin or valproate</td>
</tr>
<tr>
<td>&gt;120 min</td>
<td>Stage III-refractory SE</td>
<td>IV general anesthesia, propofol, midazolam, phenobarbitone</td>
</tr>
<tr>
<td>&gt;24 h</td>
<td>Stage IV-supra refractory SE</td>
<td>Inhalation anesthesia</td>
</tr>
</tbody>
</table>
Alternative Therapy: Pharmacological

- Ketamine
- Topiramate
- Corticosteroids
- IVIG or Plasma Exchange
- Inhaled anesthetics
- Magnesium
- High dose phenobarbital
Why Ketamine?

• Mechanism of Action
  – GABA A receptors internalized, NMDA receptor gain as SE ensues
• Low incidence of Hypotension
• IV anesthetic with relatively good availability
• May contribute to increase in ICP
• Psychiatric effects??
• 60 episodes of RSE and KET use
• Permanent control in 36/60 (57%)
• KET contributed to control in 19/60 (32%)

• **Predictor of efficacy:** fewer than 7 failed drugs
• **Minimum effective dose:** 0.9 mg/kg/hr

• Discontinued due to adverse effects in 5
• **Predictor of adverse effects:** 2 or more concurrent anesthetics
• Overall mortality rate 43%
Immunomodulation

- Increasing recognition of anti-neuronal abs as cause of RSE
- Evidence of the role of inflammation in SE
- May have a role without known immunologic disease
- Methylprednisolone 1 g/day for 3-5 days or IVIG
- Longer term IVIG, Plasma exchange or immunomodulatory agents if response

Questions:
- How early to start??
- Short and long term effects
Alternative Therapy: Non-pharmacological

- Vagus nerve stimulation
- Ketogenic diet
- Hypothermia
- Electroconvulsive therapy
- Transcranial magnetic stimulation
- Surgical management
Ketogenic Diet

- Retrospective series, adults with SRSE, 4 centers
- 10 cases; 4 male, 7 encephalitis
- Median SE duration 21 days, AEDs: 7
- 90% achieved ketosis and all seizure cessation at median 3 days
- 3 minor complications: acidosis, Incr. TG
- 2 died (unrelated to KD)

Thakur, Neurology 2014
Questions That Remain

• Defining non-convulsive status epilepticus by EEG

• How aggressive to treat?
  – Seizure burden

• How long to treat?
Better Terminology Still Needed:
Definition of NCSE vs. NCS?

• Not clearly defined
• 30 minutes of continued electrographic seizure activity?
• Seizure Burden: >50% of a given epoch?
• The point at which neuronal injury occurs?
1 Hour QEEG: 5/hour, 4 channels at maximum extent
71 yo Right Parietal GBM presented with fever and confusion
71 yo Right Parietal GBM presented with fever and confusion
An hour later after treatment.....
The Ictal-Interictal Continuum
Prolonged Refractory SE (> 7 days)

- 63 pts identified, ages 14-86

<table>
<thead>
<tr>
<th>Duration (days)</th>
<th>Survival at Hospital Discharge</th>
<th>Outcome: mRS 3 or better at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-30</td>
<td>31/42 (74%)</td>
<td>5/31 (16%)</td>
</tr>
<tr>
<td>30-59</td>
<td>6/13 (46%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>60-89</td>
<td>4/4 (100%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>1/3 (33%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*survival and outcome was not age-dependent

Killbride et al, Neurocritical Care 2013
Summary

• RSE is common
• Identify and treat underlying etiology
• Faster treatment = better outcomes regardless of treatment used
• Outcome is not always dismal
• Prospective studies and better defined protocols are needed