The Management of Status Epilepticus - 2013

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Disclosures

• None
Self assessment questions
Q1 - Which of the following is true regarding the cooperative VA status epilepticus trial?

A. Lorazepam was superior to phenytoin
B. Subtle generalized convulsive status epilepticus was easier to control than overt convulsive status epilepticus
C. Response to second agent was as good as response to first agent
D. 30 day mortality was ~65% for overt status and 27% for subtle status.
Q2- Which of the following is not true of prehospital treatment of status?

A. IV lorazepam was less effective than IM midazolam
B. IV lorazepam was more effective than placebo
C. IV lorazepam had a greater odds ratio versus placebo than IV diazepam
D. Respiratory complications are greater with benzodiazepine than placebo use
Q3- which is true for second-line treatment of SE?

A. IV valproate is less effective than IV phenytoin
B. IV levetiracetam is less effective than IV valproate
C. IV lacosamide is more effective than IV levetiracetam
D. IV phenobarbital is an appropriate second-line agent in focal motor simple partial status epilepticus
Q4- Choose the incorrect answer

A. IV lorazepam has a longer duration of action than IV diazepam
B. Lorazepam has a longer half-life than diazepam
C. IV lorazepam is less likely to redistribute in adipose tissue than diazepam
D. IV diazepam has a faster onset of action than diazepam
Status Epilepticus- operational definition (criterion for initiation of therapy)

Status epilepticus is

- 5 minutes of continuous epileptic seizure activity (10 min for children younger than 5 years)

or

- 2 or more sequential seizures without full recovery of consciousness between the seizures
Rationale for operational definition of status epilepticus

• Operational definition based on generalized tonic-clonic seizures (focal or generalized onset)
• Traditional definition was 30 minutes
• However, generalized tonic-clonic seizures rarely last longer than 2 minutes (whether focal or generalized onset)
• GTC seizure lasting longer than 2 minutes will likely evolve to status epilepticus
Duration of first unprovoked seizure in 407 children. Probability of a seizure that has continued to time (t) stopping. The longer a seizure lasts, the less likely it is to stop spontaneously.  
Shinnar, Ann Neurol 2001
Seizure type and type of status epilepticus (based on the ILAE classification)

<table>
<thead>
<tr>
<th></th>
<th>Convulsive</th>
<th>Non-convulsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>I- Partial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Simple</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>B. Complex</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>C. 2arily Generalized</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>II- Generalized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Absence</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>B. Myoclonic</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>C. Clonic</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>D. Tonic</td>
<td>+</td>
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<tr>
<td>E. Tonic-Clonic</td>
<td>+</td>
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<tr>
<td>F. Atonic</td>
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<td>+</td>
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<tr>
<td>SEIZURE TYPE</td>
<td>STATUS TYPE</td>
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<td>-------------------</td>
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<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>Overt convulsive</td>
<td></td>
</tr>
<tr>
<td>Tonic clonic</td>
<td>Subtle convulsive</td>
<td></td>
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<tr>
<td>Partial</td>
<td>Nonconvulsive</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td></td>
<td></td>
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</tbody>
</table>
Overt vs Subtle SE in VA study

- Overt generalized status epilepticus: easily visible generalized convulsions
- Subtle status epilepticus: indicated by coma and ictal discharges on the electroencephalogram, with or without subtle convulsive movements such as rhythmic muscle twitches or tonic eye deviation

<table>
<thead>
<tr>
<th></th>
<th>Overt</th>
<th>Subtle</th>
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</thead>
<tbody>
<tr>
<td><strong>Response to 1st IV drug</strong></td>
<td><strong>55.5%</strong></td>
<td><strong>14.9%</strong></td>
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<tr>
<td>Motor Activity</td>
<td>Consciousness</td>
<td>Generalized</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Intense (convulsive)</td>
<td>Markedly to severely impaired</td>
<td>Tonic-clonic</td>
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<tr>
<td></td>
<td></td>
<td>Tonic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonic</td>
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<tr>
<td></td>
<td></td>
<td>Myoclonic (with absence, or in coma)</td>
</tr>
<tr>
<td></td>
<td>Normal to mildly impaired</td>
<td>Myoclonic (usually in primary generalized epilepsy)</td>
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<tr>
<td>Absent or subtle (nonconvulsive)</td>
<td>Markedly to severely impaired</td>
<td>Absence (including typical, atypical, and late-onset)</td>
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<tr>
<td></td>
<td></td>
<td>Subtle or purely electrographic (in coma)</td>
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<tr>
<td></td>
<td>Normal to mildly impaired</td>
<td>Absence (including typical, atypical, and late-onset)</td>
</tr>
</tbody>
</table>
Incidence of SE for the total pediatric adult and elderly populations in Richmond

DeLorenzo RJ, J Clin Neurophysiol 1995
<table>
<thead>
<tr>
<th>ETIOLOGY</th>
<th>CHILDREN</th>
<th>ADULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Acute symptomatic</td>
<td>35%</td>
<td>50%</td>
</tr>
<tr>
<td>Febrile</td>
<td><strong>25%</strong></td>
<td>0%</td>
</tr>
<tr>
<td>Remote symptomatic</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Progressive encephalopathy</td>
<td>5%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Relationship of status and epilepsy

- 10% of patients who develop epilepsy present with status
- 25% of status occurs in patients with epilepsy
- 15% of persons with epilepsy experience status epilepticus
More than 50% of people who develop status have no history of epilepsy
Generalized convulsive status epilepticus

• Generalized tonic-clonic seizure that does not stop or series of generalized tonic-clonic seizures without recovery of consciousness in between seizures.

• Does not require EEG for diagnosis

• Clonic activity becomes less prominent over time, and may stop even while electrographic seizure activity continues on EEG (subtle generalized convulsive status epilepticus)
Pathophysiology of status and brain injury

• Systemic factors
  – Hypoxia, hypoglycemia, hypotension, hyperthermia, acidosis

• Cerebral metabolic factors

• Excitotoxic cerebral injury
Systemic metabolic factors in prolonged convulsions in primates (Meldrum, 1983)

- Early
  - Increased systolic and diastolic BP
  - Increased cerebral venous pressure
  - Metabolic (lactic) acidosis

- After 15-65 minutes
  - Increased glucose
  - Increased temperature
  - Mixed acidosis

- Late
  - Variable hypotension
  - Hypoglycemia
Systemic metabolic factors in prolonged convulsions in primates (Meldrum, 1983)

The occurrence of neuronal damage correlated with the duration of seizures and hyperpyrexia, but not with the severity of early systemic metabolic derangements.
How early do irreversible neuropathological changes appear?

In 15-30 minutes:
  Microvacuolation
  Mitochondrial changes
    (swelling, disruption of cristae)
### Neurophysiology
- **Early Status Epilepticus**
  - Receptor trafficking:
    - GABA and NMDA
- **Refractory Status Epilepticus → Malignant Status Epilepticus**
  - Early synaptic plasticity:
    - Modification of GABA receptor composition
  - Altered gene expression:
    - Receptors
    - Drug transporters and drug resistance proteins

### Motor Activity
- Generalized convulsions
  - Myoclonus
  - Electromechanical dissociation

### Systemic Pathology
- **Compensatory Phase (Sympathetic Overdrive)**
  - Cardiac output
  - Blood pressure
  - Blood glucose
  - Blood lactate
- ** Decompensation (Homeostatic Failure)**
  - Cardiac output
  - Blood glucose
  - Blood lactate
  - Blood oxygen
  - Cardiorespiratory collapse
  - Electrolyte imbalances
  - Rhabdomyolysis and delayed tubular necrosis
  - Hyperthermia
  - Multiple organ failure

### Brain Metabolism
- Cerebral blood flow
- Glucose and oxygen
- Brain tissue oxygenation
- Brain glucose

### Brain Damage
- Convulsive
- Nonconvulsive
Status epilepticus:
Guidelines for therapy

1- Have a plan
2- Treat intravenously
3- Therapeutic endpoint is cessation of seizure activity in the brain
4- Be prepared to ventilate
5- Use adequate doses- treat all patients (including those with epilepsy) with same regimens
6- Intensive nursing care is required
Therapy of status epilepticus

- ABCs: ensure airway and O$_2$, maintain blood pressure, monitor cardiac function
- Obtain baseline blood studies and establish IV access
- Give glucose IV (if low or unable to measure)
- Administer antiepileptic drugs
- Obtain diagnostic studies
If you document hypoglycemia or cannot get a glucose measurement:

- **Adults**
  - Administer 100 mg of thiamine followed by 50 ml of 50% glucose

- **Children**
  - Administer 2 ml/Kg of 25% glucose
Drugs effective in convulsive status epilepticus

BENZODIAZEPINES
  Diazepam
  Lorazepam
FOSPHENYTOIN (PHENYTOIN)
PHENOBARBITAL
VALPROATE
LEVETIRACETAM, LACOSAMIDE
DRUG THERAPY TO AVOID

INEFFECTIVE DRUGS
Narcotics
Neuroleptics
Neuromuscular blockers (without seizure control)

INEFFECTIVE ROUTES OF ADMINISTRATION
IM Phenytoin (However, IM Fosphenytoin is an option if IV access not possible)
DIAZEPAM

Initial dose 0.15-0.25 mg/Kg
Maximal rate of administration 5 mg/min
Expected time to stop status 1-3 min
Duration of action 15-30 min
Major side effects
  Depression of consciousness for 10-30 minutes
  Occasional respiratory depression
  Infrequent hypotension
LORAZEPAM

Initial dose 0.1 mg/Kg
Maximal rate of administration 2 mg/min
Expected time to stop status 6-10 min
Duration of action >12-24 hours

Major side effects
- Depression of consciousness for several hours
- Occasional respiratory depression
- Infrequent hypotension
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<tbody>
<tr>
<td><strong>FOSPHENYTOIN</strong></td>
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<tr>
<td><strong>Initial dose (PE)</strong></td>
<td>15-20 mg/Kg</td>
</tr>
<tr>
<td><strong>Maximal rate of</strong></td>
<td></td>
</tr>
<tr>
<td>administration (adult)</td>
<td>150 mg/min</td>
</tr>
<tr>
<td>child: 3mg/kg/min</td>
<td></td>
</tr>
<tr>
<td><strong>Expected time to stop</strong></td>
<td></td>
</tr>
<tr>
<td>status</td>
<td>10-30 min</td>
</tr>
<tr>
<td><strong>Duration of action</strong></td>
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<td></td>
<td>&gt;24 hours</td>
</tr>
<tr>
<td><strong>Major side effects</strong></td>
<td></td>
</tr>
<tr>
<td>Occasional hypotension (elderly)</td>
<td></td>
</tr>
<tr>
<td>Pruritis (not relevant in convulsive status epilepticus)</td>
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</tbody>
</table>
PHENOBARBITAL

Initial dose: 20 mg/Kg
Maximal rate of administration: 100 mg/min
Expected time to stop status: 10-30 min
Duration of action: >48 hours

Major side effects:
- Depression of consciousness for hours to days
- Occasional respiratory depression
- Infrequent hypotension
Comparison of 4 treatment protocols for status epilepticus (Treiman et al, 1996)

• Four intravenous regimens:
  – Lorazepam alone (0.1 mg per kg)
  – Phenytoin alone (18 mg per kg)
  – Diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg)
  – Phenobarbital alone (15 mg per kg)

• 570 patients enrolled- 518 patients had verified generalized convulsive status epilepticus (384 overt, 134 subtle)

• For overt SE, lorazepam alone was superior to phenytoin alone when assessed at 20 minutes after beginning administration (verified diagnosis- pairwise comparison- p=0.002).

• There were no differences among the treatments with respect to recurrence during the 12-hour study period, the incidence of adverse reactions, or the outcome at 30 days.
A Patients with Verified Diagnoses

Successful Treatment (%)

- Lorazepam: Overt 64.9, Subtle 17.9
- Phenobarbital: Overt 58.2, Subtle 24.2
- Diazepam and Phenobarbital: Overt 55.8, Subtle 8.3
- Phenobarbital: Overt 43.6, Subtle 7.7

No. of Patients
- Overt: 97, 91, 95, 101
- Subtle: 39, 33, 36, 26
## Response in VA study

<table>
<thead>
<tr>
<th></th>
<th>Overt</th>
<th>Subtle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st agent</td>
<td>55.5%</td>
<td>14.9%</td>
</tr>
<tr>
<td>2nd agent</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>3rd agent</td>
<td>2.3%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>
Refractory status epilepticus

- Diagnosed after failure of 2 drugs or status for >60-90 minutes
- Definition adopted in NCS guidelines: failure to respond to two AEDs.
  - up to 40% of cases
- Predictors: encephalitis, hypoxic-ischemic
- encephalopathy, delayed diagnosis and treatment, and subtle status epilepticus
Treatment of refractory status: anesthesia

- **BARBITURATES**
  - Phenobarbital
  - Pentobarbital
  - Pentothal

- **Benzodiazepines**
  - Diazepam drip
  - Midazolam (Versed) drip

- **Propofol** (Diprivan)

- **Ketamine**
Which anesthetic?

- Midazolam associated with a higher rate of breakthrough seizures (tachyphylaxis)
- Pentobarbital associated with more frequent hypotension
- Prolonged infusion of propofol can lead to acidosis, multiple organ failure, and rhabdomyolysis (propofol infusion syndrome).
  - Risk factors: prolonged administration (>48 hours), high dose (>5 mg/kg/h), young age, acute neurologic illness.
Vanderbilt proposed guidelines

• If anesthesia is expected <24 hours, midazolam or propofol are preferable due to short half-life and rapid recovery after discontinuation.

• If anesthesia is required for longer durations, switch to pentobarbital within 24 hours of anesthesia onset.
  – Prolonged midazolam use is associated with tachyphylaxis
  – Propofol should not be used for >24 hours

• If duration of anesthesia is predicted >24 hours, pentobarbital is the preferable agent and is titrated to burst suppression. If there is cessation of EEG ictal activity, pentobarbital should be stopped within 24-48 hours of initiation.
Pentobarbital

- Recovery from anesthesia is expected to be slower due to pentobarbital accumulation in adipose tissue and may take up to one week. After pentobarbital withdrawal, the EEG may show PLEDs (periodic lateralized epileptiform discharges) or GPEDs (generalized periodic epileptiform discharges) for up to several days. Unless this is the same EEG pattern that led to anesthesia treatment for status epilepticus, this pattern should be watched but not be cause for resumption of pentobarbital.
De novo generalized periodic discharges (GPDs) related to anesthetic withdrawal (GRAWs) resolve spontaneously
Convulsive Status Epilepticus Treatment

5 min
- GTC Sz > 5 min
- Status Epilepticus clinically diagnosed
- Out of hospital treatment
  - IV lorazepam
  - IV diazepam
  - IM midazolam

30 min
- Seizures on ED arrival
- Established status epilepticus
- Second line therapy
  - fosphenytoin 20 mg/kg IV
  - valproate 30 mg/kg IV
  - levetiracetam 30-60 mg/kg IV

60 min
- Seizures continue, patient not responding
- Refractory status epilepticus
- Intubation, cEEG initiated
- Third line therapy
  - midazolam
  - propofol
  - pentobarbital

24 hr
- Seizures continue during or after anesthesia withdrawal
- Super-refractory status epilepticus
- Other antiepileptic medications, ketamine, immunomodulation, hypothermia, surgery, VNS, ketogenic diet, etc.
Dosing suggestions for other AEDs

- Lacosamide 200-400 mg IV
- Levetiracetam 1000-3000 mg IV
- Valproate 20-40 mg/kg IV
- Topiramate 200-500 mg NG/PO
- Pregabalin, oxcarbazepine, felbamate are also options
Alternatives when IV therapy is not available

• Rectal drug administration
  – Diazepam
  – Lorazepam
  – (Paraldehyde)

• IM drug administration
  – Fosphenytoin
  – Diazepam

• Intranasal administration
  – Midazolam (0.2 mg/kg, 5 mg/ml solution dropped by syringe into both nostrils in equal doses)

• Buccal administration
  – Midazolam (0.3 mg/kg)
Responsiveness of status & timing of treatment (Lowenstein & Alldredge 1993)

- Treatment within 30 minutes of onset: status stopped by first line therapy in 80% of patients
- Treatment started ≥ 2 hours after onset: status stopped by first line therapy in <40% of patients
GABA$_A$ receptors ($\gamma$-containing) are internalized during status epilepticus.

Relative loss of synaptic $\gamma$-containing GABA$_A$ receptors is likely responsible for decreased effectiveness of benzodiazepines with increasing seizure duration.

NMDA receptor surface expression increases contributing to increased excitatory drive.
Diazepam was effective in controlling brief (10 min) seizures but lost efficacy after prolonged (45 min) seizures.
Early treatment is essential

- Treat acute repetitive seizures (risk factor for SE)
- Prehospital treatment with rectal diazepam was associated with a shorter duration of status after arrival to the emergency department, even when SE was still present (Chin et al., 2008).
- 2 mg of IV lorazepam by paramedics was associated with termination of status before arrival to the emergency room in 59.1% of individuals, compared to 21.1% treated with placebo (Alldredge et al., 2001).

- Randomized, double-blind trial to evaluate intravenous benzodiazepines administered by paramedics for the treatment of out-of-hospital SE
- IV diazepam (5 mg), lorazepam (2 mg), or placebo. An identical second injection was given if needed.
- SE had been terminated on ER arrival in more patients treated with lorazepam (59.1 percent) or diazepam (42.6 percent) than patients given placebo (21.1 percent) (P= 0.001).

- Odds ratio for termination of SE with LZP vs PCB was 4.8; LZP vs DZP 1.9; DZO vs PCB 2.3
- Rates of respiratory or circulatory complications 10.6% for LZP, 10.3% for DZP; 22.5% for PCB
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th><strong>LORAZEPAM GROUP</strong> (N=66)</th>
<th><strong>DIAZEPAM GROUP</strong> (N=68)</th>
<th><strong>PLACEBO GROUP</strong> (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>
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</table>

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<thead>
<tr>
<th></th>
<th><strong>LORAZEPAM vs. PLACEBO</strong></th>
<th><strong>LORAZEPAM vs. DIAZEPAM</strong></th>
<th><strong>DIAZEPAM vs. PLACEBO</strong></th>
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</thead>
<tbody>
<tr>
<td>Odds ratio (simultaneous 95 percent CI) for termination of status epilepticus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted</td>
<td>5.4 (2.3–13.2)</td>
<td>1.9 (0.9–4.3)</td>
<td>2.8 (1.2–6.7)</td>
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<tr>
<td>Adjusted†</td>
<td>4.8 (1.9–13.0)</td>
<td>1.9 (0.8–4.4)</td>
<td>2.3 (1.0–5.9)</td>
</tr>
</tbody>
</table>
**Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART)**

- IM autoinjector midazolam vs. IV lorazepam therapy for prehospital status epilepticus
- 73.4% in IM midazolam group vs. 63.4% in IV lorazepam group had stopped seizing by arrival in the ED
- Median time to active treatment was 1.2 minutes in the midazolam group vs. 4.8 min in the IV lorazepam group
- In IM midazolam group, significant increase in percentage of patients discharged from ED and reduction in ICU admissions.

*Silbergleit et al., NEJM, 2012*
Out of hospital treatment

- Intramuscular midazolam - 0.15-0.3 mg/Kg
- Rectal diazepam, 0.5 mg/Kg (up to 20 mg)
- Intramuscular autoinjector diazepam
- Intranasal or buccal midazolam, 0.2 mg/kg
Place of valproate, levetiracetam, lacosamide

- Valproate may be as effective or more effective than phenytoin
- Levetiracetam less effective than valproate in retrospective analysis (Alvarez 2011)
- Lacosamide efficacy is still being evaluated
VPA vs PHT in status epilepticus: a pilot study  Misra et al, Neurology. 2006

- 68 patients with convulsive status epilepticus (SE) were randomly assigned to two groups.
- VPA 30 mg/kg in 100 mL saline infused over 15 minutes versus PHT 18 mg/kg in 100 mL saline infused at rate of 50 mg/minute.
- Patients were crossed over if first drug not effective
- Seizures were aborted in 66% in the VPA group and 42% in the PHT group.
- As a second choice in refractory patients, VPA was effective in 79% and PHT was effective in 25%.
- Side effects in the two groups did not differ.
Randomized study of IV VPA and PHT in status epilepticus Agarwal et al, Seizure. 2007

- 100 patients with benzodiazepine refractory SE
- IV VPA 20 mg/kg at rate 40 mg/min or IV PHT 20 mg/kg, max. rate of 50 mg/min after dilution with normal saline.
- All patients were earlier given IV diazepam 0.2 mg/kg at 2 mg/min up to a maximum of 20 mg before labeling as refractory to diazepam.
- Treatment was considered successful when all motor or EEG seizure activity ceased within 20min after the beginning of the drug infusion and no return of seizure activity during the next 12h.
- IV VPA was successful in 88% and IV PHT in 84% (p>0.05)
- Significantly better response in patients with SE <2h (p<0.05)
PHT vs VPA vs LEV - Alvarez, Epilepsia 2011

• 187 SE episodes in which PHT, VPA, or LEV were given after benzodiazepines.
• VPA failed to control SE in 25.4%, PHT in 41.4%, and LEV in 48.3% of episodes.
• LEV failed more often than VPA
• PHT was not statistically different from VPA or LEV
Table 67.7 Protocol for Treatment of Status Epilepticus Used at Vanderbilt University

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Treatment Details</th>
</tr>
</thead>
</table>
| 0-15 min     | IV: normal saline at TKO  
If blood glucose low: 1 amp D_{50} (50 mL IVP) and start second IV with D_{50}NS  
Thiamine 100 mg IVP if given D_{50} or if cachectic/malnourished/alcoholic  
If actively seizing:  
Lorazepam IV, 10 mg at <2 mg/min  
Fosphenytoin, max. delivery rate = 150 mg/min, total dose 20 mg/kg  
  - Do not use if status is due to a metabolic cause unlikely to respond to phenytoin  
  - Reduce delivery rate if AV block or hypotension  
  - Current treatment with phenytoin is not a contraindication |
| 15-60 min    | For patients with decreasing seizures after fosphenytoin load: additional 10 mg/kg of fosphenytoin  
For patients continuing to seize who require intubation:  
  - Thiopental ± succinylcholine (avoid succinylcholine if possible)  
  - Consider additional dose of fosphenytoin 10 mg/kg  
For continuing seizures post intubation:  
  - Midazolam: 0.3 mg/kg by slow IV injection, may repeat at 5-min intervals ×3 doses. Midazolam infusion starts at 2 µg/kg/min; increase by 1 µg/kg/min every 15 min until seizure activity stops  
    - or -  
  - Propofol: 1-2 mg/kg, then 2-10 mg/kg/h  
    - or -  
  - Pentobarbital: 5 mg/kg loading dose (to achieve burst-suppression pattern on EEG with interburst intervals of approx. 7 sec); repeat load as necessary to max. of 15 mg/kg, then 1-3 mg/kg/h maintenance dose ×6-12 h; reevaluate patient  
    - or -  
  - Phenobarbital: 20 mg/kg at <100 mg/min |

AV, Atroventricular; D, dextrose; EEG, electroencephalogram; IV, intravenous; IVP, IV push; NS, normal saline; TKO, to keep open.
First phase (emergent) diagnostic studies

- Glucose, electrolytes, BUN
- Oximetry or arterial blood gases
- Antiepileptic drug levels
- Lumbar puncture (if clinically indicated)
- Complete blood count
- Urinalysis
- Toxicology screening
Second phase studies* (after stabilization)

- Liver function studies
- Toxicology screen
- EEG if the patient has not awakened
- CT or MRI scan
- EEG/Video monitoring?

* depending on the clinical situation
Role of EEG

- EEG is essential to identify electrographic SE in patients who fail to regain consciousness after a gen tonic-clonic seizure or SE and in patients with nonconvulsive status epilepticus without prior overt clinical seizure activity.

- NCS guidelines recommend cEEG ($\geq$24 hrs) in patients at high risk of nonconvulsive seizures and NSE ($\sim$2/3 nonconvulsive seizures are missed with a routine EEG).
164 prospective patients were evaluated at the MCV NCU Status Epilepticus Program.

Continuous EEG monitoring was performed for a minimum of 24 h after clinical control of CSE.

After CSE was controlled 48% demonstrated persistent electrographic seizures. More than 14% of the patients manifested NCSE predominantly of the complex partial NCSE seizure type.

These patients were comatose and showed no overt clinical signs of convulsive activity. Clinical detection of NCSE in these patients would not have been possible with routine neurological evaluations without use of EEG monitoring.
Institution of long term therapy

- The decision to initiate long term therapy should be individualized.
- In low risk or debatable situations, patients should know their options.
Long term therapy

- Not indicated
  - Acute symptomatic seizures (drug intoxication, electrolyte imbalance, alcohol withdrawal)
- Debatabe
  - Febrile seizure
  - First idiopathic seizure is status
- Indicated
  - Structural brain abnormality
  - Progressive neurological disorder
  - Idiopathic seizure with epileptiform EEG
Status epilepticus: mortality

Barry and Hauser, 1992
Outcome of status epilepticus is related to

- The cause of the seizures
- Age of the patient
- Duration of status
- Treatment
Sequelae of convulsive status epilepticus

- None
- Residual neurological disability
  - Mental handicap
  - Motor deficit
  - Sensory deficit
  - Epilepsy
- Death
Mortality of status epilepticus: relation to duration and age

DeLorenzo et al, 1992
Other forms of status epilepticus

- Simple partial: avoid general anesthesia-use agents that do not depress consciousness
- Complex partial: delay intubation & general anesthesia by using additional fosphenytoin, then IV valproate, ?IV levetiracetam, IV lacosamide before using phenobarbital
- Absence status: benzodiazepine, then valproate
- Myoclonic status: benzodiazepine, then valproate (?levetiracetam)
Nonconvulsive status epilepticus

• Requires EEG for diagnosis
• EEG interpretation should be combined with clinical data
• Keep in mind progression of EEG patterns with persistent status epilepticus
Self assessment questions
Q1 - Which of the following is true regarding the cooperative VA status epilepticus trial?

A. Lorazepam was superior to phenytoin

B. Subtle generalized convulsive status epilepticus was easier to control that overt convulsive status epilepticus

C. Response to second agent was as good as response to first agent

D. 30 day mortality was ~65% for overt status and 27% for subtle status.
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Q2- Which of the following is not true of prehospital treatment of status?

A. IV lorazepam was less effective than IM midazolam
B. IV lorazepam was more effective than placebo
C. IV lorazepam had a greater odds ratio versus placebo than IV diazepam
D. Respiratory complications are greater with benzodiazepine than placebo use
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Q3- which is true for second-line treatment of SE?

A. IV valproate is less effective than IV phenytoin
B. IV levetiracetam is less effective than IV valproate
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D. IV phenobarbital is an appropriate second-line agent in focal motor simple partial status epilepticus
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Q4- Choose the incorrect answer

A. IV lorazepam has a longer duration of action than IV diazepam
B. Lorazepam has a longer half-life than diazepam
C. IV lorazepam is less likely to redistribute in adipose tissue than diazepam
D. IV diazepam has a faster onset of action than diazepam
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