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Treatment of Acute Seizures and Status Epilepticus

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Status Epilepticus: Definition

- 1876 Bourneville: “more or less incessant seizures”
- 1962 Gastaut: “persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition”
- 1993 EFA: Single or recurrent seizures without recovery lasting >30 minutes
- Working definition (Lowenstein): 5 minutes
“Continuous seizure for at least 5 minutes (>10 minutes in children) or two or more seizures without full recovery of consciousness”

ILAE Task Force

“Status epilepticus” (ILAE Task Force 2015)\(^1\)

- “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 \(t_1\)). It is a condition which can have long-term consequences (after time point \(t_2\)), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.”
  - \(t_1\)=time point beyond which the seizure should be regarded as “continuous seizure activity”
  - \(t_2\)=time of ongoing seizure activity after which there is a risk of long-term consequences

### Sample Classification of Status Epilepticus

<table>
<thead>
<tr>
<th>Type</th>
<th>Seizure Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convulsive status epilepticus</td>
<td>Primary generalized</td>
</tr>
<tr>
<td></td>
<td>Simple partial (SPSE or epilepsia partialis continua)</td>
</tr>
<tr>
<td></td>
<td>Complex partial (CPSE with motor involvement)</td>
</tr>
<tr>
<td></td>
<td>Secondarily generalized</td>
</tr>
<tr>
<td>Nonconvulsive status epilepticus in the ambulatory population (NCSE-A)</td>
<td>Primary generalized (eg, typical absence)</td>
</tr>
<tr>
<td></td>
<td>SPSE</td>
</tr>
<tr>
<td></td>
<td>CPSE</td>
</tr>
<tr>
<td></td>
<td>Secondarily generalized</td>
</tr>
<tr>
<td>Nonconvulsive status epilepticus in the comatose or critically ill (NCSE-C)</td>
<td>Focal</td>
</tr>
<tr>
<td></td>
<td>Bilateral/generalized</td>
</tr>
<tr>
<td>Myoclonic status epilepticus (MSE)</td>
<td>Primary MSE (in primary generalized epilepsy)</td>
</tr>
<tr>
<td></td>
<td>Secondary MSE (in symptomatic generalized epilepsy)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic (eg, after cardiac arrest)</td>
</tr>
</tbody>
</table>

CPSE: Complex partial status epilepticus
SPSE: Simple partial status epilepticus
Epidemiology

• Overall incidence of status epilepticus
  • 10.3 – 61/100,000
  • 33% – 71% of these are GCSE
  • 75% of GCSE present as overt GCSE

• 3 million cases of status epilepticus worldwide
• 2 million cases of GCSE worldwide

**Common Etiologies of Status Epilepticus in Adults**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsant noncompliance</td>
<td>29%</td>
</tr>
<tr>
<td>Alcohol related (predominantly withdrawal)</td>
<td>26%</td>
</tr>
<tr>
<td>CNS infection</td>
<td>8%</td>
</tr>
<tr>
<td>Refractory epilepsy</td>
<td>6%</td>
</tr>
<tr>
<td>Trauma</td>
<td>6%</td>
</tr>
<tr>
<td>Tumor related</td>
<td>6%</td>
</tr>
<tr>
<td>Acute stroke</td>
<td>6%</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>4%</td>
</tr>
<tr>
<td>Acute hypoxic-ischemic encephalopathy</td>
<td>4%</td>
</tr>
<tr>
<td>Miscellaneous and undetermined</td>
<td>6%</td>
</tr>
</tbody>
</table>

### Etiologies of Status Epilepticus in Children

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remote symptomatic epilepsy</td>
<td>27%</td>
</tr>
<tr>
<td>Acute symptomatic seizures</td>
<td>22%</td>
</tr>
<tr>
<td>Febrile</td>
<td>17%</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>14%</td>
</tr>
<tr>
<td>CNS infection</td>
<td>11%</td>
</tr>
<tr>
<td>Acute metabolic disorders</td>
<td>5%</td>
</tr>
<tr>
<td>Miscellaneous diagnosed causes</td>
<td>4%</td>
</tr>
</tbody>
</table>

SE Etiology and Mortality

- Epilepsy
- Alcohol/Drug withdrawal
- Toxic-metabolic
- Idiopathic

1%-3% Mortality

- Hypoxic-ischemic injury
- Acute stroke
- Tumor
- Trauma
- CNS Infection

20%-30% Mortality
Treatment: Main Principles

• Stop ongoing seizures quickly (clinical and electrographic)
• Prevent recurrences
• Minimize complications
• Consider how quickly AEDs cross Blood-Brain-Barrier
Stages of Status Epilepticus

- Duration/refractoriness of status epilepticus
  - **Early status epilepticus (Pre-hospital stage)**
    - 0 – 30 minutes
  - **Established status epilepticus**
    - 31 – 120 minutes
    - Failure to respond to benzodiazepine
  - **Refractory status epilepticus**
    - 2 – 24 hours
    - Failure to respond to initial benzodiazepine and second appropriate AED
  - **Super-refractory (malignant) status epilepticus**
    - >24 hours
    - Failure to respond to anesthetic

Stages of Status Epilepticus

1. Pre-hospital
2. Established Status
3. Refractory Status
4. Super Refractory Status
Stages of Status Epilepticus

- Pre-hospital
- Established Status
- Refractory status
- Super Refractory Status
Why Pre-hospital Treatment?

• Longer duration of status associated with poorer outcome
• Status becomes more refractory with time
• It is treatable!
Pre-hospital Treatment Options

• Favorable Rescue Medications:
  • Easy and quick administration
  • Convenient to carry around
  • Quick penetration of blood-brain barrier
  • Short half life for quicker recovery

• Rectal diazepam gel: commercially available
• Intramuscular (midazolam, diazepam) and intranasal (midazolam) forms of benzodiazepines under active clinical study
Parenteral Benzodiazepines

**Diazepam**
- 0.2 mg/kg dosing
- 5 mg/min IV push
- Very highly lipophilic
- Rapid BBB penetrance
- Elimination $T_{1/2} = 48$ hours
- Redistribution $T_{1/2} = 60$ minutes
- Short effective CNS $T_{1/2}$

**Lorazepam**
- 0.1 mg/kg
- 2 mg/min
- Slightly less lipid soluble
- Redistribution $T_{1/2} = 2-3$ hours; strongly bound to bzd receptor
- Longer effective CNS $T_{1/2}$; little accumulation in lipid stores
Pre-hospital Treatment: PHTSE Trial

Proportion of Patients in Status Epilepticus

Minutes

Placebo
Diazepam
Lorazepam

P < 0.001

Pre-hospital Treatment: PHTSE Trial


• Results

• Benzodiazepines given out-of-hospital in SE are safe (% of cardiopulmonary complications):
  • Lorazepam group: 10.6%
  • Diazepam group: 10.3%
  • Placebo: 22.5%

• Benzodiazepines given out-of-hospital in SE are effective

Midazolam

- Fast-acting benzodiazepine
- Half-life of 1.2 to 12.3 hours
- Dosage
  - 0.2 mg/kg over 5 min
  - Maintenance infusion 0.05-2.0 mg/kg/h
- Comparative benefits
  - Hypotension occurs less frequently than with propofol or barbiturates
  - Intravenous, intramuscular, sublingual, intranasal
Pre-hospital Treatment: RAMPART Study

• Intramuscular vs. Intravenous Therapy for Pre-Hospital Status Epilepticus
  • Double-blind, randomized, noninferiority trial
    • IM midazolam
    • Intravenous lorazepam
  • Subjects with seizures lasting >5 minutes and still seizing on arrival
  • Administered by paramedics
  • Primary outcome: Absence of seizures on arrival to ED
  • Secondary Outcomes
    • Intubation
    • Recurrent Seizures
    • Timing of treatment relative to seizure cessation

Pre-hospital Treatment: RAMPART Study


- **Results:**
  - **IM midazolam is noninferior to IV lorazepam**
    - Post hoc analysis demonstrated IM midazolam superiority
  - **IM midazolam treatment group had higher rate of discharge from emergency department**
    - Similar or lower rates of recurrent seizures
    - Similar or lower rates of endotracheal intubation
Stages of Status Epilepticus

- Pre-hospital
- Established Status
- Refractory status
- Super Refractory Status
## Status Epilepticus Treatment Algorithm

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Ensure adequate ventilation/O2</td>
</tr>
<tr>
<td></td>
<td>Thiamine 100 mg, 50% glucose 25 mg IV</td>
</tr>
<tr>
<td>2-3 min.</td>
<td>IV line with NS, rapid assessment, blood draw</td>
</tr>
<tr>
<td>4-5 min.</td>
<td>Lorazepam 0.1 mg/kg</td>
</tr>
<tr>
<td>7-8 min.</td>
<td>Phenytoin or Fosphenytoin 20 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>at $\leq 50$ mg/min Phenytoin or 150 mg/min Fosphenytoin</td>
</tr>
</tbody>
</table>

**VA Cooperative Study 1998**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Successful treatment (%)</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>64.9</td>
<td>97</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>58.2</td>
<td>91</td>
</tr>
<tr>
<td>Diazepam and Phenytoin</td>
<td>55.8</td>
<td>95</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>43.6</td>
<td>101</td>
</tr>
</tbody>
</table>

**No. of Patients**

- **Overt**: 97, 91, 95, 101
- **Subtle**: 39, 33, 36, 26

**IV Phenytoin**

- Effective in terminating Generalized Convulsive Status Epilepticus
- Lacks significant CNS depression
- Vehicle (propylene glycol) may cause hypotension
- pH=13 - tissue necrosis if infiltrates
- Cardiac monitoring required. Slow rate if QT interval increases or hypotension or arrhythmias

**Fosphenytoin**

- Water soluble phosphate ester of phenytoin
- Must be cleaved to phenytoin prior to effect
- Rapidly converts after IV or IM
- 8-15 minute to convert to active form
- May be given up to 150 mg/min
- ECG, BP and respiratory monitoring
Treatment of Status: The Branch Point

Seizures Stop; Patient Wakes Up

Seizures Don’t Stop
Convulsions Stop; Patient Doesn’t Wake Up
Clinical Features That Suggest SE

- Coma with subtle multifocal myoclonic movements
- Coma alone
- Eye deviation, Thumb twitching
- Nystagmoid eye jerks
- Hippus
- Abrupt decline in level of consciousness
- “Twilight state,” especially with cycling of behavior between less responsive and more responsive states
EEG Patterns That Suggest SE

• Clearly ictal
  • Repeated isolated szs with typical evolution but without recovery between ictal events

• Probably ictal
  • Repeated or continuous rhythmic spikes or sharp waves, sometimes followed by slow wave; focal or generalized

• Possibly ictal
  • PLEDs, biPLEDs, PEDs, triphasic waves, burst-suppression patterns, paroxysmal slowing
<table>
<thead>
<tr>
<th>EEG Patterns</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic Lateralized Epileptiform Discharges (PLEDs)</td>
<td>Ischemic infarcts, tumors, encephalitis, old lesions with recent seizures</td>
</tr>
<tr>
<td>Bilateral Independent PLEDs (BIPEDs)</td>
<td>Hypoxic encephalopathy, encephalitis, meningitis, chronic epilepsy</td>
</tr>
<tr>
<td>Periodic Epileptiform Discharges (PEDs)</td>
<td>Metabolic encephalopathy, anoxia-ischemia, convulsive SE, degenerative disease</td>
</tr>
<tr>
<td>Triphasic Waves (TWs)</td>
<td>Hepatic encephalopathy, renal encephalopathy</td>
</tr>
</tbody>
</table>
Resolving Ambiguous Patterns

2 mg Lorazepam Given
Phase 1 – Discrete Seizures

Phase 2 – Merging Seizures

Phase 3 – Continuous Ictal Activity

Phase 4 – Continuous Ictal Activity with Flat Periods

Phase 5 – Periodic Epileptiform Discharges

Stages of Status Epilepticus

1. Pre-hospital
2. Established Status
3. Refractory status
4. Super Refractory Status
Refractory Status Epilepticus

- Failure of first line therapy followed by a second line therapy (benzodiazepine + phenytoin)
- Occurs in 10%-40% of cases of status
- Serious consequences:
  - Respiratory failure
  - Pneumonia
  - Sepsis
  - Hypotension
  - Prolonged hospital stays
  - Higher mortality rate
Refractory Status Epilepticus

- Transformation from prolonged seizure to self-sustaining status epilepticus
- Self-sustaining status in animals
- Status epilepticus induced neuronal damage evident
- Pharmacoresistance develops
Refractory Status Epilepticus

- Switch from lack of inhibition to increased excitation
- Change in receptor affinity for benzodiazepines

Survival and Duration of SE


- % Survival
- N=253
- OR 17.2 (4.1-72)
- \( P = .0001 \)

Length of Seizure
- \(<1 \text{ hour}\)
- \(>1 \text{ hour}\)

Days

% Survival

- 100
- 90
- 80
- 70
- 60

Survival and Duration of SE

RSE Treatment

**IV Phenobarbital**
- Loading dose: 20 mg/kg at 50 mg/min infusion
- Adverse effects: hypotension, sedation, infection, paralytic ileus

**IV Valproate**
- Mean efficacy: 75.7% (95% CI: 63.7%–84.8%)
- Hyperammonemia, hepatic/pancreatic toxicity, platelet dysfunction
- Loading 20-40 mg/kg at 1.5-3 mg/kg/min

**IV Levetiracetam**
- Loading 30-70 mg/kg at 500 mg/min
- Mean efficacy: 68.5% (95% CI: 56.2%–78.7%)
- No significant adverse effects and well tolerated across age groups

**IV Lacosamide**
- Readily available in IV (200 mg/20 ml per vial)
- Dosage: 200-400 mg over 15 min
- Efficacy: 75%-100%

RSE Treatment

• **IV Midazolam**
  - Short acting benzodiazepine
  - Maintenance dose: 0.05-2.9 mg/kg/h
  - Response: 82% (37% at 48 h)
  - Adverse effects: hypotension, respiratory suppression, tachyphylaxis

• **IV Propofol**
  - GABA$_A$ agonist, NMDA inhibitor, Ca$^{++}$ influx modulation
  - Maintenance dose: 2-15 mg/kg/h
  - Response: 67%-73% (54% at 48 h)
  - Adverse effects: hypotension, respiratory suppression, propofol infusion syndrome

• **IV Pentobarbital**
  - Barbiturate – active on GABA$_A$ receptors without γ2 subunit
  - Maintenance dose: 0.5-10 mg/kg/h
  - Response: 92% (57% at 48 h)
  - Adverse effects: hypotension, respiratory suppression

Treatment Comparison

- **Misra UK, et al. 2006**
  - 68 untreated patients with GCSE randomized to IV phenytoin or IV valproate
  - Seizure abortion: valproate – 66% (79%); phenytoin – 42% (25%)

- **Agarwal P, et al. 2007**
  - 100 patients with benzodiazepine refractory GCSE randomized to IV phenytoin or IV valproate
  - Seizure abortion: valproate – 88% (57%); phenytoin – 84% (40%)

- **Gilad R, et al. 2008**
  - 74 adult with SE randomized to IV phenytoin or IV valproate
  - Seizure abortion: valproate – 87.8%; phenytoin – 88% (12% with adverse effects)

- **Alvarez V, et al. 2011**
  - 187 episodes of SE in adults who were treated initially with benzodiazepines received IV phenytoin, IV valproate, or IV levetiracetam
  - Seizure *abortion failure*: valproate – 25.4%; phenytoin – 41.4%; levetiracetam – 48.3%

Treatment Comparison

- Claassen J, et al. 2002
  - Systematic review of 193 patients
  - Breakthrough seizures were more frequent in midazolam group
  - Barbiturates administration resulted in burst suppression more frequently (96%)

- Rossetti AO, Lowenstein DH. 2011
  - Prospective, randomized controlled trial of 23 patients
  - Seven-day seizure freedom was similar between propofol and barbiturates
  - Patients receiving barbiturates had longer mechanical ventilation time

- Unknown at this time
  - Difference in survival among patients on different general anesthetics
  - Difference in survival between patients with burst suppression and seizure control
  - Duration of suppression

Treatment Algorithm to Consider

**Impending and early SE (5-30 min)**
- **Intravenous benzodiazepine**
  - Lorazepam 0.1 mg/kg, or clonazepam 0.015 mg/kg, or midazolam 0.2 mg/kg

**Established and early refractory SE (30 min-48 h)**
- **Intravenous antiepileptic drug**
  - Phenytoin 20 mg/kg, or valproate 20-30 mg/kg, or levetiracetam 20-30 mg/kg
- **Intravenous midazolam**
  - 0.2 mg/kg → 0.2-0.6 mg/kg/h and/or
- **Intravenous propofol**
  - 2 mg/kg → 2-10 mg/kg/h

**Late refractory SE (>48 h)**
- **Pentobarbital (thiopental)**
  - 5 mg/kg (1 mg/kg) → 1-5 mg/kg/h
- **Other drugs**
  - Lidocaine, verapamil, magnesium, immunomodulation
- **Other anesthetics**
  - Isoflurane, desflurane, ketamine

**Other approaches**
- Surgery, VNS, rTMS, ECT, hypothermia, ketogenic diet

**Established and early refractory SE (30 min-48 h)**
- **Focal-complex, myoclonic, or absence SE**
  - **Further intravenous or oral antiepileptic drug**
    - Valproate, levetiracetam, lacosamide, topiramate, pregabalin, or other
# Etiologies of Refractory Status Epilepticus

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>19%</td>
</tr>
<tr>
<td>Pre-existing epilepsy</td>
<td>18%</td>
</tr>
<tr>
<td>Metabolic</td>
<td>13%</td>
</tr>
<tr>
<td>Acute stroke</td>
<td>11%</td>
</tr>
<tr>
<td>Tumor related</td>
<td>10%</td>
</tr>
<tr>
<td>Alcohol or other drug withdrawal</td>
<td>9%</td>
</tr>
<tr>
<td>Drug intoxication</td>
<td>6%</td>
</tr>
<tr>
<td>Acute hypoxic-ischemic encephalopathy</td>
<td>6%</td>
</tr>
<tr>
<td>Acute trauma</td>
<td>6%</td>
</tr>
<tr>
<td>Miscellaneous or undetermined</td>
<td>2%</td>
</tr>
</tbody>
</table>

Bleck TP. *Epilepsy Curr.* 2010.
RSE: Think Possible Autoimmune Disorders

- Anti-NMDA receptor limbic encephalitis
  - Antiglutamate receptor limbic encephalitis
- Antineuronal antibody syndromes with limbic encephalitis
- Paraneoplastic limbic encephalitis, without a demonstrable antibody
- Limbic encephalitis with other triggers
  - Following various systemic viral infections
  - Following various viral vaccines
  - Associated with drug hypersensitivity reactions
- Other autoimmune processes
  - Hashimoto’s encephalopathy (autoimmune thyroid encephalopathy)
  - Anti GAD
  - Anti VGKC
  - Systemic lupus erythematosus
  - Antiglycolipid autoantibody syndrome

SE Treatment for Autoimmune Etiology

- Acute treatment, “diagnostic test”
  - IV methylprednisolone or
  - IVIG or
  - Plasma exchange
- If diagnosis confirmed
  - Continue acute IV therapy, and taper or
  - Oral prednisone taper or
  - Oral azathioprine or oral mycophenolate mofetil
  - Or other options

Stages of Status Epilepticus

Pre-hospital → Established Status → Refractory status → Super Refractory Status
Phasic vs Tonic GABA$_A$ Receptors

Benarroch EE. Neurology. 2007.
RSE: Changes in GABA$_A$ Receptor Dynamics

Revised PKC phosphorylation and GABA$_A$ receptor internalization in repeated seizures (status epilepticus).
## Phasic vs Tonic $\text{GABA}_A$ Receptors

<table>
<thead>
<tr>
<th>$\gamma_2$ subunit</th>
<th>$\delta$ subunit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clustered at synaptic site (interaction with gephyrin)</td>
<td>Spread through extrasynaptic membrane</td>
</tr>
<tr>
<td>Responds to synaptic-released GABA</td>
<td>Responds to “ambient” GABA</td>
</tr>
<tr>
<td>Positive modulation: benzodiazepines</td>
<td>Positive modulation: neurosteroids, general anesthetics and alcohol</td>
</tr>
<tr>
<td>Phasic inhibition</td>
<td>Tonic inhibition</td>
</tr>
<tr>
<td>Regulates network interaction in cerebral cortex</td>
<td>Regulates cell excitability</td>
</tr>
<tr>
<td>Fast internalization during SE</td>
<td>Slow internalization during SE</td>
</tr>
</tbody>
</table>

Allopregnanolone for SRSE

- The neurosteroid allopregnanolone (SAGE-547) acts as a positive allosteric modulator of synaptic and extrasynaptic GABA$_A$ receptors.
- Clinical studies for adults and children with SRSE are underway

Glutamate Receptors

- **AMPA**
  - Four subunits
  - GluR1 – GluR4
  - GluR2 subunit: no Ca\(^{++}\) permeability

- **NMDA**
  - Four subunits
  - NR1, NR2A, NR2B
  - NR2B: slower decay than NR2A

- **Kainate**

AMPAR Receptors

- AMPA-receptor plasticity
  - Up-regulation
    - Flip/flop versions
    - Flip: slower decay
  - Subunit composition alteration
    - GluR1/GluR2 composition
    - GluR1: permeable to $\text{Ca}^{++}$
    - GluR2: not permeable to $\text{Ca}^{++}$

NMDA Receptors

- NMDA-receptor plasticity
  - Activated by repetitive activity
    - Mg^{++} block removed
  - Subunit composition alteration
    - NR1-NR2B up regulation (slower decay)
- Presynaptic receptor up regulation
  - Facilitates glutamate release

# AMPA vs NMDA Receptors

<table>
<thead>
<tr>
<th>Glutamate Ionotropic Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMPA</strong></td>
</tr>
<tr>
<td>Permeability: Na⁺, K⁺, (Ca++)</td>
</tr>
<tr>
<td>Main contributor to EPSP</td>
</tr>
<tr>
<td>Brief duration of action</td>
</tr>
<tr>
<td>Fast decay</td>
</tr>
<tr>
<td>Prompt desensitization</td>
</tr>
<tr>
<td>Structural plasticity: normal/abnormal</td>
</tr>
</tbody>
</table>

**Super-Refractory SE Treatment**

- **Ketamine** 0.5-4.5 mg/kg IV bolus (up to 5 mg/kg/h infusion)
- **Topiramate** per orogastric tube
  - 300-1600 mg/day in adults
- **Isoflurane or desflurane or gabapentin or levetiracetam**
- **Magnesium** infusion 4 g IV bolus, 2-6 g/h infusion
- **Pyridoxine** 180-600 mg/d IV or per orogastric tube
- **Steroids**, 1 g/d IV x 3 days, followed by 1 mg/kg/d (1 week)
- **Immunoglobulin**, 0.4 g/kg/d IV for 5 days or plasmapheresis

Super-Refractory SE Treatment

- Hypothermia of 32-35°C for less than 48 hours
- Ketogenic diet 4:1
- Neurosurgical resection of epileptic focus
- Electroconvulsive therapy
- VNS or DBS
- Transcranial magnetic stimulation (TMS)

Outcomes

Convulsive status epilepticus

**Mortality**
- At hospital discharge: 9%-21%
- At 30 days: 19%-27%
- At 90 days: 19%

**Morbidity**
- Severe neurological/cognitive sequelae: 11%-16%
- Functional status deterioration: 25%

**Factors associated with poor outcome**
- Underlying etiology
- De novo SE
- Older age
- Impairment of consciousness
- Duration of seizures
- Focal signs at onset
- Medical complications

**Outcomes**

**Convulsive status epilepticus**

- Mortality
  - At hospital discharge: 9-21%
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  - At 90 days: 19%

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- Factors associated with poor outcome
  - Underlying etiology
  - De novo SE
  - Older age
  - Impairment of consciousness
  - Duration of seizures
  - Focal signs at onset
  - Medical complications

**Nonconvulsive status epilepticus**

- Mortality
  - At hospital discharge: 18%-52%
  - At 30 days: 65%

- Factors associated with poor outcome
  - Underlying etiology
    - 27% mortality (known medical cause)
    - 3% mortality (no known medical cause)
  - Severe mental status impairment
  - Longer seizure duration
    - <10 hours: 10% mortality
    - >20 hours: 85% mortality

Outcomes

**Convulsive status epilepticus**

- **Mortality**
  - At hospital discharge: 9-21%
  - At 30 days: 19-27%
  - At 90 days: 19%

- **Morbidity**
  - Severe neurological/cognitive sequelae: 11-16%
  - Functional status deterioration: 25%

- **Factors associated with poor outcome**
  - Underlying etiology
  - De novo SE
  - Older age
  - Impairment of consciousness
  - Duration of seizures
  - Focal signs at onset
  - Medical complications

**Nonconvulsive status epilepticus**

- **Mortality**
  - At hospital discharge: 18-52%
  - At 30 days: 65%

- **Factors associated with poor outcome**
  - Underlying etiology
    - 27% mortality (known medical cause)
    - 3% mortality (no known medical cause)
  - Severe mental status impairment
  - Longer seizure duration
    - <10 hours: 10% mortality
    - >20 hours: 85% mortality

**Refractory status epilepticus**

- **Mortality**
  - At hospital discharge: 23%-61%
  - At 90 days: 39%

- **Morbidity**
  - Meyer et al (2002) - 13 survivors:
    - Vegetative state: 23%
    - Severely disabled: 62%
    - Moderately disabled (independent): 15%
    - Post-SE epilepsy: 88%

- **Factors associated with poor outcome**
  - Underlying etiology
  - Older age
  - Long seizure duration
  - High APACHE-2 scores

Things to Remember

• The sooner you treat SE, the better the outcome
• Understand the dynamic changes of GABA and glutamate receptors
• Medication has to readily cross the blood-brain barrier
• Minimize the complications