Outline

- Definition of status epilepticus
- Classification of status epilepticus
- Treatment of status epilepticus
- Treatment of NCSE
- Treat underlying etiology
- Treating seizure-related complications
- Outcome
Definition of status epilepticus
ILAE 2015

- Condition resulting either from failure of mechanisms responsible for seizure termination or from initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1)

- Condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on type and duration of seizures

Operational dimension with $t_1$ indicating time that emergency treatment should be started and $t_2$ indicating the time at which long term consequences may be expected.

<table>
<thead>
<tr>
<th>Type of SE</th>
<th>Time ($t_1$)</th>
<th>Time ($t_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic-clonic</td>
<td>5 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Focal SE with impaired consciousness</td>
<td>10 min</td>
<td>&gt;60 min</td>
</tr>
<tr>
<td>Absence status</td>
<td>10-15 min</td>
<td>unknown</td>
</tr>
</tbody>
</table>

Classification of epilepsy

- Semiology
- Etiology
- EEG correlates
- Age
Classification of SE: semiology

Table 2. Axis 1: Classification of status epilepticus (SE)

(A) With prominent motor symptoms
A.1 Convulsive SE (CSE, synonym: tonic-clonic SE)
   A.1.a Generalized convulsive
   A.1.b Focal onset evolving into bilateral convulsive SE
   A.1.c Unknown whether focal or generalized
A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
   A.2.a With coma
   A.2.b Without coma
A.3 Focal motor
   A.3.a Repeated focal motor seizures (Jacksonian)
   A.3.b Epilepsia partialis continua (EPC)
   A.3.c. Adverse status
   A.3.d Oculofacioclonic status
   A.3.e. Ictal paresis (i.e., focal inhibitory SE)
A.4 Tonic status
A.5 Hyperkinetic SE
(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B.1 NCSE with coma (including so-called "subtle" SE)
B.2 NCSE without coma
   B.2.a Generalized
      B.2.a.a Typical absence status
      B.2.a.b Atypical absence status
      B.2.a.c Myoclonic absence status
   B.2.b Focal
      B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
      B.2.b.b Aphasic status
      B.2.b.c With impaired consciousness
   B.2.c Unknown whether focal or generalized
      B.2.c.a Autonomic SE

Etiology of status epilepticus

- Known (i.e., symptomatic)
  - Acute (stroke, intoxication, malaria, encephalitis)
  - Remote (posttraumatic, postencephalitis, poststroke)
  - Progressive (brain tumor, Lafora’s disease, PME, dementia)
  - SE in defined electroclinical syndromes

- Unknown (i.e., cryptogenic)

EEG correlate

- No evidence-based EEG criteria for SE
- Propose following terminology to describe EEG patterns in SE
  - Location
  - Name of pattern
  - Morphology
  - Time-related features
  - Modulation
  - Effect of intervention (medication) on EEG
Age

- Neonatal (0-30 days)
- Infancy (1 mo-2 yrs)
- Childhood (> 2-12 yrs)
- Adolescence and adulthood (> 12-59 yrs)
- Elderly (≥ 60 yrs)

---

**Table 5. SE in selected electroclinical syndromes according to age**

<table>
<thead>
<tr>
<th>SE occurring in neonatal and infantile-onset epilepsy syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic status (e.g., in Ohtahara syndrome or West syndrome)</td>
</tr>
<tr>
<td>Myoclonic status in Dravet syndrome</td>
</tr>
<tr>
<td>Focal status</td>
</tr>
<tr>
<td>Febrile SE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SE occurring mainly in childhood and adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)</td>
</tr>
<tr>
<td>NCSE in specific childhood epilepsy syndromes and etiologies (e.g., Ring chromosome 20 and other karyotype abnormalities, Angelman syndrome, epilepsy with myoclonic-ataxic seizures, other childhood myoclonic encephalopathies; see Appendices 1, 3)</td>
</tr>
<tr>
<td>Tonic status in Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>Myoclonic status in progressive myoclonus epilepsies</td>
</tr>
<tr>
<td>Electrical status epilepticus in slow wave sleep (ESES)</td>
</tr>
<tr>
<td>Aphasic status in Landau-Kleffner syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SE occurring mainly in adolescence and adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonic status in juvenile myoclonic epilepsy</td>
</tr>
<tr>
<td>Absence status in juvenile absence epilepsy</td>
</tr>
<tr>
<td>Myoclonic status in Down syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SE occurring mainly in the elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonic status in Alzheimer’s disease</td>
</tr>
<tr>
<td>Nonconvulsive status epilepticus in Creutzfeldt-Jakob disease</td>
</tr>
<tr>
<td>De novo (or relapsing) absence status of later life</td>
</tr>
</tbody>
</table>

These forms of SE may be encountered prevalently in some age groups, but not exclusively.
Epidemiology

- Incidence of SE reportedly ranges from 10-40 per 100,000 in various databases

- Peak incidence occurs at < 10 year (14.3 per 100,000) and > 50 year (28.4 per 100,000)

- Highest mortality in elderly population

- Increasing number of patients with SE over past 10 year
  - Increased detection of NCSE in ICU
  - Aging of population
  - Less rigid definition of SE
Age-specific incidence and in-hospital mortality with Status Epilepticus

Crude Incidence of Status Epilepticus (per 100,000)

Decade of life

In-hospital mortality with Status Epilepticus (percent)

Staging of status epilepticus

- Premonitory
  - confusion, myoclonus, increased seizure frequency
- Incipient 0-5 min
- Early: 5-30 min
- Transition: from early to established
- Established (late): 30-60 min
- Refractory SE: after 60 min
- Postictal
5 EEG stages of SE during course of GCSE

A. Discrete seizures with interictal slow
B. Waxing and waning of ictal discharge
C. Continuous ictal activity
D. Continuous ictal activity punctuated by flat period
E. Periodic discharges on 'flat' BG

EEG stages predict treatment response in experimental SE

Comparison of time to stage I and stage III treatment
Shaded boxes indicate time periods in which stage I and stage III onsets overlap
In this overlap, all treatments of stage I were successful, whereas those of stage III were not successful, despite sharing similar SE durations

Treatment of status epilepticus

- Emphasize time to treatment rather than a certain sequence of medications
- Treat underlying etiology
- Treating seizure-related complications and preventing seizure recurrence
Treatment

- Prehospital: benzodiazepine

- Emergency department, in patient: second line agent

- ICU
  - 0.1 mg/kg lorazepam followed by third-line agent
  - Second line AEDs → to prevent return of seizures when weaning off anesthesia
Proposed treatment algorithm for status epilepticus


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 ECG 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

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 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 (0.2-0.3 mg/kg, max: 20 mg/dose, single dose, Level B) OR
   Intranasal midazolam (Level B), buccal midazolam (Level B)

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 (60 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)

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, propofol, or propofol (all with continuous EEG monitoring).

Initial treatment: stabilization, 0-5 min

- ABC
- Time seizure, vital sign
- Assess oxygenation
- ECG monitoring
- Finger stick glucose
- IV access, electrolyte, hematology, toxic screen, AEDs level
Initial treatment: AEDs

- Treatment of early SE relies on use of benzodiazepines
  - Lorazepam, diazepam, midazolam, clonazepam

- Benzodiazepine
  - Enhancing inhibitory neurotransmission through increasing channel opening frequency of GABA-A receptors, subsequent increased chloride conductance and neuronal hyperpolarization
Prehospital treatment

- IM midazolam 0.2 mg/kg
- IV lorazepam 0.1 mg/kg
- IV diazepam 0.15-0.2 mg/kg
  - Less optimal pharmacokinetic profile
  - Alternate to both IV lorazepam and IM midazolam
- Intranasal midazolam 0.2 mg/kg
- Buccal midazolam 0.5 mg/kg
  - Emerged as first-line non-IV drug in children with similar efficacy
- Rectal diazepam 0.2-0.5 mg/kg
Lorazepam

- Less lipid-soluble and not undergo a rapid redistribution into peripheral tissues → longer duration of action → higher seizure control

- No statistically significant difference between these 2 drugs in respiratory failure/depression
Diazepam

- Highly lipophilic, rapidly passes brain–blood barrier
- Subsequently redistributed into peripheral tissues with only 3–5% of total dose remaining in brain
- Rapid, but transient antiepileptic effect

Route
- IV
- per rectum (PR)
- IM: slow with a long time to peak serum concentration of 1 hr
- IV and PR → higher efficacy for seizure cessation and lower risk of adverse effects compared to placebo
First line AEDs data, class I study

- 1998, US Department of Veterans Affairs Cooperative Study RCT
  - 570 patients, lorazepam, DZP followed by PHT, PHT, PB
  - IV lorazepam 0.1 mg/kg, 2 mg/min was superior as compared to IV phenytoin as first-line therapy in aborting SE
    - 64.9% aborted with IV lorazepam
    - 43.5% with IV phenytoin

- 2001 study: 2mg IV lorazepam, 5 mg IV DZP, placebo
  - Lorazepam and DZP superior to placebo
First line AEDs data, class I study

- 2012 Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) data → better efficacy for IM midazolam than for standard IV lorazepam because of speed and ease of administration
  - IM midazolam (10 mg) stopped seizures in 73.4%
  - IV lorazepam (4 mg) stopped seizures in 63.4%

- Secondary analysis of this study conducted only in patients < 18 years found no difference between IM midazolam and IV lorazepam
  - Relatively few children study
Conclusion: Adult

- IM midazolam, IV lorazepam, IV diazepam (with or without phenytoin), and IV PB are established as efficacious at stopping seizures lasting at least 5 min (level A).

- No significant difference in effectiveness between lorazepam and diazepam (level A).

- IM midazolam has superior effectiveness compared with IV lorazepam with convulsive SE without established IV access (level A).

- IV lorazepam is more effective than IV PHT in stopping seizures lasting at least 10 min (level A).
Conclusion: Children

- IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 min (level A)
- Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 min (level B)
- Insufficient data exist in children about efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy (level U)
### Summary: Initial treatment

#### 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 ECG 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

#### 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 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
- Intranasal midazolam (Level B), buccal midazolam (Level B)

---

Emergency Department/Inpatient Treatment

- IV access

- Full 0.1 mg/kg of lorazepam can be administered at 2 mg/min first-line therapy to best terminate SE

- Second-line therapy with IV AEDs
Second line AEDs

- Phenytoin/fosphenytoin
- Phenobarbital
- Valproate
- Levetiracetam
- Lacosamide
Phenytoin

- High lipid soluble, water insoluble

- Prepared in an alkaline polypropylene solvent with a pH of ~12 to prevent precipitation of substance → local irritation and thrombophlebitis at infusion site

- 18–20 mg/kg in younger adult, 15 mg/kg in elderly (>65 yr)

- Maximum infusion rate of 50 mg/minute

- Risk of cardiac arrhythmias, infusion site reactions, hypotension, liver induction

- Less sedating side effect profile compared to PB
Fosphenytoin

- Highly water soluble, phenytoin prodrug
- Completely absorbed (bioavailability 100%)
- Dosages of fosphenytoin are expressed as PHT equivalents (PE), IV rates of 100–150 mg PE/min → bioequivalent to 50 mg/min PHT

Advantages
- Availability for IM injection
- Rapid than IV administration
- Lower risk of adverse effects at injection sites

Disadvantages: High costs
Phenobarbital

- Efficacy: 73.6% (95% CI: 58.3–84.8%)

- Disadvantages
  - Respiratory depression, arterial hypotension, deep sedation, tolerance effects, drug interactions
Valproate

- Broad spectrum of efficacy against all seizure types
- Well tolerated even in critically ill patients, in high doses and fast infusion rates
- Non-sedating
- Overall response rate of 70.9%
- Effective dose 15–45 mg/kg in bolus (6–10 mg/kg/minute) followed by 1–3 mg/kg/h infusion
- Low incidence of adverse events overall (<10%)
  - Dizziness, thrombocytopenia, mild hypotension
  - Acute encephalopathy
  - Liver failure
  - Pancreatitis
Levetiracetam

- Broad spectrum AED with a low potential of interactions, due to minimal hepatic metabolism and low plasma protein binding (<10%)
- Very low rate of adverse effects
  - Most often somnolence, sedation, rarely agitation, thrombocytopenia
- Efficacy ranged from 44-94%
Lacosamide

- Enhancing slow inactivation of voltage-gated sodium channels
- Current evidence on IV use in acute seizures and SE is restricted to (retrospective) case reports and case series
- Most commonly loading dose 200-400 mg over 5-10 min, followed by daily dose of 200–400 mg leading to abrogation of seizures in 56%
- Adverse events reported in 25%
  - Mild sedation (25 patients), angioedema (one), allergic skin reactions (two), hypotension (four), pruritus (one), third-degree AV block (one), paroxysmal asystole
- To date, there is not enough evidence to recommend lacosamide routinely in treatment of established SE
Second line AEDs

- No RCT has specifically evaluated efficacy of different sequences of IV AEDs
- Medication choices are based on comorbid conditions, side effects, and opinions
Second line AEDs data

- Available evidence suggests some degree of efficacy for IV valproate, levetiracetam, lacosamide.

- A meta-analysis of 8 studies, 294 episodes of SE
  - Higher rates of seizure cessation with VPA and PB > LEV, PHT
    - VPA 75.7% (95% CI 63.7–84.8)
    - PB 73.6%, (95% CI 58.3–84.8)
    - LEV 68.5% (95% CI 56.2–78.7)
    - Phenytoin 50.2% (95% CI 34.2–66.1)

- Favorable tolerability profile of LEV, VPA

Second line AEDs data

- In adult
  - IV VPA has similar efficacy to IV PHT or continuous IV diazepam (level C)
  - Insufficient data exist in adults about efficacy of LEV as either initial or second therapy (level U)

- In children
  - IV VPA has similar efficacy but better tolerability than IV PB (level B)
  - Insufficient data exist in children regarding efficacy of phenytoin or LEV (level U)
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 (60 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)
Third line therapy for RSE

- No clear evidence to guide therapy
- AEDs should be initiated in a time-dependent fashion
  - SE treatment becomes less effective as longer episode of SE lasts
  - 0.1 mg/kg lorazepam followed immediately by third-line agent
Refractory SE

- NCS tend to last much longer than convulsive seizures are more difficult to treat
  - NCS has 15% response to first medication
  - GCSE has 55% response rate overall to first medication and 60-70% when medication given in prehospital setting

- Continuous EEG
  - Titrate medication to burst suppression
  - Monitor for seizure activity
Refractory SE: medication

- Continuous midazolam infusion are most widely used (59%) followed by propofol (32%) and barbiturates (8%)
- Choices are largely based on availability and comorbid conditions
- Typically, weaned off third-line agent after 24-48 hrs
Midazolam

- Often used as the initial choice for a third-line agent
- Less impact on blood pressure and often effective
- Less effective with prolonged use and requires an increase in dose for same effect because of degradation of GABA receptors during SE
- Often weaned off midazolam after 48 to 72 hours or transitioned to pentobarbital
Propofol

- Exact mechanisms are unknown

- Experimental evidence suggests that it acts as an N-methyl-D-aspartate (NMDA) antagonist

- Water insoluble fast acting anesthetic agent with antiepileptic properties

- Shorter duration of action, much lower tendency to accumulate in body than barbiturates

- Often available in ICU
Propofol: side effect

- Lower blood pressure
- Propofol infusion syndrome, estimated risk of 1%
  - Characterized by
    - Congestive heart failure
    - Lactic acidosis
    - Hypertriglyceridemia
    - Rhabdomyolysis
    - Renal failure
- Risk factors
  - High doses > 4 mg/kg/hour and long durations of administration > 48 hr
  - Carbohydrate depletion
  - Inborn errors of fatty acid oxidation
  - Severe illness
  - Administration of catecholamine and glucocorticosteroid
Thiopental, pentobarbital

- Barbiturates acting as γ-aminobutyric acid-A agonists with enhanced inhibitory neurotransmission and antiepileptic action
- Long half-life and takes a number of hours to reach a therapeutic level
- Prolonged duration of action, mainly due to their accumulation in body → long recovery time
- Very reliable in ability to achieve burst suppression
Thiopenthal, pentobarbital Adverse effect

- Hypotension and cardiorespiratory depression
- Profound suppression of immune system
- Increased morbidity because of prolonged duration of pentobarbital-associated comas
  - Typically last at least a week, increasing risk for DVT/pulmonary embolism, myocardial depression/reduced cardiac output, ileus complicating nutrition and any oral medication use
Inhalational anesthetics

- Isoflurane, desflurane

- Enhance GABAA activity, inhibit NMDA receptor

- Adverse effect
  - Hypotension
  - Infection, paralytic ileus, DVT
  - Questionable cognitive dysfunction with prolonged use
Super-refractory SE

- Ongoing seizure activity or recurrence of seizure 24 hours or more after initiation of anesthetic therapy, including seizure recurrence on reduction or withdrawal of anesthesia

- No RCTs for treatment of super-refractory SE exist
Super-refractory SE

- Pharmacological treatment
  - Ketamine
  - AEDs
  - Magnesium
  - Lidocaine
  - Anti-inflammatory drug and steroid

- Non-pharmacological option
  - Ketogenic diet
  - Hypothermia
  - Electroconvulsive therapy
  - Transcranial magnetic stimulation
  - Vagus nerve stimulator
Treatment of super-refractory SE

First 24 hours

Early status epilepticus
Established status epilepticus
Refractory status epilepticus

Next days to weeks

Super-refractory status epilepticus

FIND CAUSE

- Full panoply of ICU care including respiratory & cardiovascular support +/− Hypothermia
- Continued anaesthesia (with conventional anaesthetics or ketamine)
- Conventional AEDs (wide choice) = use 2 - 3 AEDs at high dose and avoid too frequent switching
- Magnesium infusion
- Steroids +/− IVIG +/- PL exchange
- Consider other physical therapies

Shorvon S. Epilepsia 2011;52 Suppl 8:53-6.
AEDs

- Topiramate (93 cases; 5 mg/kg in children, 500–1000 mg daily dose in adults)
- Lacosamide (71 cases; 200 to 400 mg daily dose)
- Levetiracetam (35 cases; 15-70 mg/kg in children, 30-70 mg/kg in adults)
- Pregabalin (23 cases; mean dose 350 mg)
- Perampanel (22 cases; initial median 4 mg were titrated up to median 12 mg)
Choices AEDs

- Patient’s risk factors
- Pharmacokinetic and pharmacodynamic of drug
- Avoiding agents with high drug–drug interaction
- Oral administration
  - Reduced absorption and gastric emptying in critically ill patient
Ketamine

- Strong antagonistic effect on N-methyl-D-aspartate (NMDA) – glutamate receptor and an additional neuroprotective potential
- Half-life of 2-3 hours
- Extensively metabolized by hepatic cytochrome P450 pathway to active metabolite, norketamine
- Overall success rate was 63%
- Hemodynamic advantages
- Adverse effects: tachycardia, acute elevation BP, increased ICP
Magnesium sulfate

- Currently used as drug of choice in treating seizures occurring in eclampsia
- Little evidence for efficacy in treatment of RSE in absence of hypomagnesemia or eclampsia
- Blocking glutamatergic N-methyl-D-aspartate (NMDA) receptor in resting state
Lidocaine

- Local anesthetic agent and a cardiac depressant used as an antiarrhythmic agent
- Effect as sodium channel blockers in neuronal membranes
- No single RCTs conducted to evaluate efficacy and safety of lidocaine in patients with SE
Anti-inflammatory drugs and steroids

- Evidence supporting use of steroids, immunoglobuline, and plasma exchange in super-refractory SE without a proven or suspected underlying immunological disorder is extremely scarce.

- Potential side effects: immunosuppression, severe infections and metabolic disturbances.
Neuroactive steroid: allopregnanolone

- Positive allosteric modulator of synaptic and extrasynaptic GABA-A receptors
- Efficacy of allopregnanolone in cessation of established SE observed in animal models
- In humans, only one case report of two pediatric patients with super-refractory SE with cessation of seizure activity
- Currently randomized, double-blind, placebo-controlled trial with neurosteroid SAGE-547 administered as a continuous intravenous infusion in Super-Refractory Status Epilepticus is recruiting since June 2015
# General dosing recommendation for SE

<table>
<thead>
<tr>
<th>Medication</th>
<th>Loading Dose</th>
<th>Maintenance</th>
<th>Half-Life</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg at a rate of 2 mg/min</td>
<td>NA</td>
<td>12 hours</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg, initial dose of 10 mg IM</td>
<td>NA</td>
<td>2-6 hours</td>
<td>Hepatic active metabolites excruted renally</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.2 mg/kg at a rate of 3 mg/min</td>
<td>NA</td>
<td>20-100 hours</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20 mg/kg IV at a rate of 50 mg/min; may reflush with another 10 mg/kg as needed</td>
<td>100 mg IV given every 6 to 8 hours</td>
<td>10-15 hours</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>20 mg PE/kg IV at a rate of 150 mg PE/kg; may reflush with another 10 mg PE/kg as needed</td>
<td>100 mg IV given every 6 to 8 hours</td>
<td>10-15 hours</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Valproate</td>
<td>20-40 mg/kg</td>
<td>4-6 mg/kg given every 6 hours</td>
<td>9-16 hours</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2000-4000 mg</td>
<td>10-15 mg/kg every 12 hours</td>
<td>7-11 hours</td>
<td>Renal excrution</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>200-400 mg</td>
<td>200-300 mg given every 12 hours</td>
<td>13 hours</td>
<td>95% Renal excrution</td>
</tr>
<tr>
<td><strong>Third line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>1.2 mg/kg</td>
<td>2.10 mg/kg/h Risk of infusion syndrome over 5 mg/kg/h for more than 48 hours</td>
<td>Rapid distribution: 2-4 minutes Slower distribution: 30-60 minutes Terminal elimination: 3-12 hours</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg</td>
<td>0.1-2 mg/kg/h</td>
<td>2-6 hours</td>
<td>Hepatic active metabolites excruted renally</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>5-10 mg/kg</td>
<td>0.5-5 mg/kg/h</td>
<td>15-50 hours</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1.5 mg/kg repeated every 5 minutes up to a dose of 4.5 mg/kg</td>
<td>2-5 mg/kg/h</td>
<td>10 minutes-2.5 hours</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

IM = Intramuscular; IV = intravenous; NA = not applicable; PE = phenytoin equivalent.
* Not US Food and Drug Administration (FDA) approved for the indication of status epilepticus.
* IV must be 16 gauge or larger and must be placed in the antecubital fossa or more proximal to prevent subcutaneous infusion necrosis (gumma growth syndrome) and venous occlusion.

Treatment of nonconvulsive status epilepticus
Major symptom of NCSE

- Altered mental status: 82%
- Speech disturbance: 15%
- Myoclonus: 13%
- Unusual behaviour: 11%
- Anxiety, agitation and/or delirium: 8%
- Extrapyramidal signs: 7%
- Hallucinations: 6%

- Memory loss: 8%
- Lethargy: 21%
- Coma: 22%
- Confusion: 49%

Unified EEG terminology and criteria for NCSE

<table>
<thead>
<tr>
<th>Table 2. Salzburg Electroencephalography Consensus Criteria for nonconvulsive status epilepticus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without known epileptic encephalopathy</td>
</tr>
<tr>
<td>EDs &gt; 2.5 Hz, or</td>
</tr>
<tr>
<td>EDs ≤ 2.5 Hz or rhythmic δ/θ activity (&gt;0.5 Hz) AND one of the following:</td>
</tr>
<tr>
<td>EEG and clinical improvement after IV AED⁹, or</td>
</tr>
<tr>
<td>Subtle clinical ictal phenomena, or</td>
</tr>
<tr>
<td>Typical spatiotemporal evolution¹¹</td>
</tr>
<tr>
<td>Patients with known epileptic encephalopathy</td>
</tr>
<tr>
<td>Increase in prominence or frequency when compared with baseline with observable change in clinical state</td>
</tr>
<tr>
<td>Improvement of clinical and EEG⁹ features with IV AEDs</td>
</tr>
</tbody>
</table>

EDs, epileptiform discharges (spikes, polyspikes, sharp-waves and sharp-and-slow-wave complexes); EEG, electroencephalography; IV AEDs, intravenous antiepileptic drugs. Reproduced with permission from [41].

⁹If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE.

¹¹Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency).

Treatment for NCSE

- Based on limited evidence and expert opinions
- Represent inferences from GCSE
- Diverse and controversial
  - Etiology
  - Type of NCSE
Treatment of NCS

- Existing data for outcome after NCS
  - 60% of pts with < 10 hours of NCS \(\rightarrow\) able to return home
  - 10 to 20 hours of NCSE \(\rightarrow\) permanent disability (50%)
  - >20 hours \(\rightarrow\) death in 85%

- Based on consensus statement and some evidence, is to treat NCS aggressively with time to seizure termination being most important goal

- SPSE, CPSE and absence SE are not usually associated with poor outcome in contrast to generalized non-convulsive SE \(\rightarrow\) avoid continuous IV anesthetic
Recommendations for treatment of NCSE in the ICU

First 2 to 5 minutes
- Emergent initial treatment
  - First-line AEDs (benzodiazepines orally, intramuscular, or intravenous bolus)

First 5 to 10 minutes
- Urgent treatment of NCSE
  - Second-line AEDs if first-line AEDs were inefficient (phenytoin, valproic acid, levetiracetam)
  - Atypical ASE and tonic SE have poor or late responses to valproic acid
  - In de novo ASE and tonic SE, benzodiazepines may worsen NCSE

First 60 minutes
- Treatment of refractory NCSE
  - Third-line non-anaesthetic AEDs first-line and second-line AEDs were insufficient (lacosamide, topiramate)
  - Consider therapeutic coma with continuous intravenous anaesthetic drugs (midazolam, propofol, barbiturates)
  - Try to avoid continuous intravenous anaesthetic drugs in SPSE, CPSE, ASE (authors’ recommendation)

Treatment of underlying disease

General management
- Noninvasive airway protection
- Monitor vital signs
- Start vasopressors with arterial hypotension
- Establish peripheral intravenous access
- Check blood glucose, blood cell count, metabolic panel, electrolytes, body temperature, toxicology-screen, AED serum levels
- EEG monitoring
- Check for patient’s medical history
- Intubation of patients with altered consciousness
- Fluid resuscitation if needed
- Neuroimaging and neurological examination
- Treatment and monitoring of underlying disease
- Check for drug interactions
- Urinary catheter
- Consider lumbar puncture

Treatment of super-refractory NCSE
- Isoflurane
- Ketamine
- Ketogenic diet

Treating underlying etiology
Addressing underlying etiology must occur concurrently with terminating seizure activity

- Acute symptomatic etiology
  - Hemorrhage, stroke, encephalitis
  - Metabolic disturbance
  - Autoimmune or paraneoplastic etiology

- Exacerbations of chronic etiologies
  - Tumor, remote stroke, TBI
Treating seizure-related complication

- Acute organ failure
- Polyneuropathy and myopathy, 30-50% of critically ill patients
- Sepsis
- DVT/pulmonary embolism
- Infections
- Aspiration
Outcome

- Some reports associate length of electrographic seizures with a poor neurologic outcome, as well as diffuse brain atrophy with prolonged seizures.

- Memory loss, psychiatric issues (paranoia, hallucinations, loss of executive function), chronic epilepsy.

- Etiology, management of complications, and time spent in SE are major determinants of short-term prognosis.

- Long term outcome: little known.
Conclusion: Status Epilepticus

- Major neurologic emergency and requires diagnostic vigilance and rapid response to prevent morbidity and mortality
- Early treatment should be emphasized over choice of medication
- No double-blind RCT study in established SE, RSE or NCSE
- Epidemiologic shift in identification of SE in inpatient population based on use of CEEG → need more data to determine long-term benefits and treatment
Future and ongoing clinical trial

- Newer drugs targeting various other mechanisms, allopregnanolone, cannabinoids or valproate derivatives

- Phase III trial in super-refractory status epilepticus (NCT02477618) June 2015-June 2017

- Phase III trial (NCT01960075) comparing efficacy of levetiracetam, valproate and fosphenytoin in established status epilepticus (Established Status Epilepticus Trial)
  - October 2015- December 2019