Status Epilepticus

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Objectives

• Define the various stages of status epilepticus and explain the proposed pathophysiology

• Explain the mechanism, side effects, and monitoring for first-, second-, and third-line treatment of SE

• Discuss medications used for refractory status epilepticus including a review of the literature

• Outline last-line therapy and future directions for super-refractory SE
Definitions

• Seizure
  - The clinical expression of abnormal, excessive, synchronous discharges of neurons residing primarily in the cerebral cortex
  - This abnormal paroxysmal activity is intermittent and usually self-limited, lasting seconds to a few minutes

• Epilepsy
  - 2 or more unprovoked seizures (>24 hours apart)
  - ILAE task force proposing revision
Prevalence and Incidence

• 1 in 10 people will have a seizure
• 1 in 100 people will have epilepsy
• 1 in 10 people with epilepsy will have intractable epilepsy

• Epilepsy: 3 million in US
  • 200,000 develop epilepsy each year
  • 45,000 are <15 years of age
Seizure Classification

- Seizure
  - Generalized
    - Convulsive
    - Non-convulsive
  - Focal/Partial
    - Simple
    - Complex
Definitions

• **Status Epilepticus (SE)**
  - Seizure lasting 5 minutes or more, or two or more sequential seizures without full recovery of consciousness to baseline between seizures
  - Historically: duration of 30 minutes or more

• **Refractory SE**
  - Persistent SE despite administration of first- and second-line agents
  - Most experts: Duration not a criteria for classification

Epidemiology

• Most common neurological emergency seen in childhood
  - Children <1 year of age
  - Adults >60 years of age

• About 60% of children are neurologically healthy prior to the first episode of SE
  - Occurs as the 1st seizure in 12% of children with epilepsy

• RSE occurs in 30-43% of patients with SE

• Overall mortality rate
  - SE: 8% in children (30% in adults)
  - RSE: 16-39%


Pediatrics
Etiology

- Etiology of SE
  - Febrile
  - Remote symptomatic, acute symptomatic
  - Cryptogenic, progressive encephalopathy, antibodies
  - AED levels

- Predictive of RSE
  - Encephalitic etiology, severe impairment of consciousness at presentation, no history of epilepsy, low AED levels in patients with known epilepsy
Differential Diagnosis

• Movement disorders
  - Spasticity
  - Clonus
  - Dystonia

• Non-epileptic seizures
  - Pseudoseizures
Initial Assessment

• Brief physical exam
  - Assess respiratory and circulatory status
  - Supportive therapy (oxygen, mechanical ventilation) as needed

• Rapid neurologic examination
  - Provide a preliminary classification of the type of SE

• Place PIV

• Ongoing monitoring of vital signs should be initiated
Initial Assessment: Labs

- Serum glucose and a rapid "finger-stick" glucose
- Serum electrolytes, calcium, and magnesium levels
- Arterial blood gases and pH
- Urine and blood toxicology – if no cause identified
- Serum antiepileptic drug (AED) levels
Initial Assessment: History

- Previous response with AED

- Missed medication
  - 1/3rd of children presenting in SE have sub-therapeutic levels

- Paradoxical effects
  - Phenytoin, carbamazepine, gabapentin, vigabatrin can precipitate generalized convulsive SE and nonconvulsive SE
  - At high serum levels, carbamazepine and phenytoin may worsen some types of seizures

- Over-the-counter, illicit substances
Goals of Treatment

• Termination of seizures
  - The risk of cerebral damage increases progressively after 1–2 hours of continuous SE
    • Result of increased excitotoxicity, hypoxia, acidosis, hypotension, multiorgan failure
  - Target underlying etiology if possible

• Prevent recurrent seizures

• Prevent or treat complications
Neurotransmitters

GABA
Main inhibitory neurotransmitter

Glutamate
Main excitatory neurotransmitter
Treatment Algorithm

- Early Status Epilepticus
- Established Status Epilepticus
- Refractory Status Epilepticus
- Super-refractory Status Epilepticus
Treatment Algorithm

Stage 1: First 30 minutes
Treat with benzodiazepines - for instance IV lorazepam, buccal midazolam, IV or rectal diazepam

Stage 2: 30-120 minutes

Stage 3: >120 minutes

After 24 hours

Established Status Epilepticus

Refractory Status Epilepticus

Super-refractory Status Epilepticus
Mechanism: Increase FREQUENCY of Cl-channel opening → hyperpolarization of membrane → decrease neuron firing
Benzodiazepines

• Lorazepam (Ativan)
  - IV/IM
  - Sublingual

• Diazepam (Valium)
  - Rectal
  - IV/IM

• Midazolam (Versed)
  - Buccal
  - Intranasal
  - IM
  - Rectal
Lorazepam

• Short-acting benzodiazepine

• Onset of action: 5 minutes (IV)

• Dose: 0.05-0.1 mg/kg (Max: 4 mg/dose)
  - IV push over 2-5 min

• Side effects
  - Sedation
  - Respiratory depression
  - Paradoxical reaction (hyperactivity)
Diazepam

• Long-acting benzodiazepine

• Onset of action: ~10 minutes (PR)

• Dose
  - 2-5 years: 0.5 mg/kg
  - 6-11 years: 0.3 mg/kg
  - ≥12 years: 0.2 mg/kg

• Side effects
  - Sedation
  - Respiratory depression
  - Paradoxical reaction (hyperactivity)
Treatment Algorithm

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- **Stage 2: 30-120 minutes**
  - Established Status Epilepticus

- **Stage 3: >120 minutes**
  - Refractory Status Epilepticus

- **After 24 hours**
  - Super-refractory Status Epilepticus
Refractory Status Epilepticus

Stage 1 - Early Status Epilepticus
Treat with benzodiazepines - for instance IV lorazepam, buccal
midazolam, IV or rectal diazepam

Stage 2 - Established Status Epilepticus
Treat with IV antiepileptic drugs – for instance, phenytoin,
phenobarbital or valproate

Stage 3: >120 minutes

After 24 hours

Super-refractory Status Epilepticus
Fosphenytoin

Mechanism: Limit the repetitive neuronal firing by blocking voltage-gated Na channels
Fosphenytoin

• Pro-drug of phenytoin
  - Dose: 30 mg PE/kg (max: 2000 mg PE/dose)
  - Dosing expressed in Phenytoin Equivalents (PE)
  - Phenytoin 1 mg = Fosphenytoin 1 mg PE

• Administration: 150 mg PE/min (up to 3 mg/kg/min)
  - Black Box Warning: faster infusion rates are related to hypotension, arrhythmias

• Levels
  - Reference range: 10-20 mcg/mL (free PHT: 1-2 mcg/mL)
  - Peak: 2 hours after Fos load (conversion to PHT complete)
  - Highly protein bound: adjust level with hypoalbuminemia
Fosphenytoin

• Local toxicity
  - “Purple glove syndrome” (discoloration with edema and pain of distal limb)
  - May or may not be associated with drug extravasation
  - Symptoms resolve spontaneously

• Sensory disturbances
  - Severe burning or itching, and/or paresthesias
  - Usually at the maximum administration rate
  - Lasts minutes-hours
  - Occurrence and intensity may be lessened by slowing or temporarily stopping the infusion
Phenobarbital

Mechanism: Increase DURATION of Cl-channel opening → hyperpolarization of membrane → decrease neuron firing

Phenobarbital

• Dose: 30 mg/kg IV
  - Max dose infants/children: 1000 mg

• Administration
  - Not to exceed 1 mg/kg/min (max 30 mg/min)
  - Respiratory depression/apnea with rapid IV
    • PICU

• Pharmacokinetics
  - Reference range: 20-40 mcg/ml
  - Potentially lethal: >80 mcg/ml
Treatment Algorithm

Stage 1: First 30 minutes
Treat with benzodiazepines - for instance IV lorazepam, buccal midazolam, IV or rectal diazepam

Stage 2: 30-120 minutes
Stage 2 - Established Status Epilepticus
Treat with IV antiepileptic drugs – for instance, phenytoin, phenobarbital or valproate

Stage 3: >120 minutes
After 24 hours

Refractory Status Epilepticus

Super-refractory Status Epilepticus
Pathophysiology of RSE

• Animal models

• Initially GABA inhibitory circuits may be deficient
  - Benzodiazepines, barbiturates: very effective early on

• Over time, GABA receptors undergo a significant shift in their ability to respond to benzodiazepines
  - Increased brain expression of drug efflux transporters P-gp at blood-brain barrier → prevent AEDs from reaching high brain concentrations
    • Phenytoin, phenobarbital, lamotrigine, levetiracetam
Pathophysiology of RSE

• Glutaminergic receptor over-activity
  - Calcium influx into the cells that triggers a cascade resulting in necrosis or apoptosis → cerebral damage
  - Usually initiated after a few hours of continuous seizure activity and thus recommended to initiate anesthesia after seizures persist for 1-2 hours
  - Antagonists of glutamate excitatory inputs (NMDA, AMPA receptors) become efficacious in the late phase

• To prevent excitotoxicity, all electrical activity should be suppressed (EEG burst-suppression)

Shorvon S, Ferlisis M. Brain 2011;134:2802-2818
Treatment Algorithm

Stage 1: First 30 minutes
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Stage 2: 30-120 minutes
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Stage 3: >120 minutes
- Refractory Status Epilepticus

After 24 hours
- Super-refractory Status Epilepticus
# Treatment Algorithm

- **Stage 1 (First 30 minutes)**
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- **Stage 2 (30-120 minutes)**
  - Established Status Epilepticus
  - Treat with IV antiepileptic drugs — for instance, phenytoin, phenobarbital or valproate

- **Stage 3 (>120 minutes)**
  - Refractory Status Epilepticus
  - Treat with general anaesthesia — for instance, propofol, midazolam, or thiopental/pentobarbital

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Super-refractory Status Epilepticus
Guidelines for RSE?

• No large prospective trials compared different treatment options for RSE

• Survey of American neurologists
  - Little agreement on third- and fourth-line therapy for RSE

• Midazolam, pentobarbital, propofol all bind to GABA$_A$ receptors $\rightarrow$ anticonvulsivant and sedative-hypnotic effects
  - Different pharmacokinetic properties and side effect profiles
Pentobarbital

- **Dose:** 5 mg/kg bolus followed by 0.5-5 mg/kg/hr

- **Advantages**
  - Long experience of use
  - Efficacy rate: 74-100%

- **Disadvantages**
  - Hydrophobic, half-life 15-50 hours
    - Risk of accumulation and long recovery time
  - Hepatic metabolism (strong CYP2A6, 3A4 inducer)
  - SE: Hypotension, cardioresp depression, immunosuppressant
    - Patient will likely require inotropic support
  - Contains propylene glycol
    - Neonates: potentially fatal metabolic acidosis, seizures
Midazolam

• Dose: 0.1-0.2 mg/kg bolus followed by 0.1-0.6 mg/kg/hr
  - Reported use up to 3 mg/kg/hr

• Advantages
  - Efficacy rate: 80-90%
  - Rapid onset and short duration of action → no accumulation

• Disadvantages
  - Strong tendency for rapid and acute tolerance
    • Seizure relapse: 47-57% of patients (2 studies)
  - Half-life prolonged: renal impairment and with CYP3A4 inhibitors
  - SE: strong respiratory depressant
  - Contains benzyl alcohol
    • “Gasping syndrome” in neonates: severe metabolic acidosis, neurologic deterioration and gasping respirations
Propofol

- Global CNS depression; GABA agonism (? Block NMDA receptor)

- Dose: 1-2 mg/kg followed by 150-200 mcg/kg/min

- Advantages
  - Different mechanism than benzodiazepines/barbiturates
  - Short half-life: rapid onset and recovery

- Disadvantages
  - Respiratory depressant, hypotension, hypertriglyceridemia
  - Drug-induced involuntary movements
  - Contraindicated with egg or soy allergy
  - Propofol infusion syndrome (PRIS)
Propofol Infusion Syndrome (PRIS)

• FDA Adverse Event Reporting System (1989-2005)
  - Deaths after propofol for non-procedural sedation
    • Respiratory disorders, suppression of seizures, control of ICP

• Common features: high dose, long infusion duration
  • Impaired utilization of fatty acid in the mitochondria
  • Acute bradycardia leading to asystole with metabolic acidosis,
    rhabdomyolysis, hyperlipidemia and/or enlarged or fatty liver
  • Risk factors: children, concomitant steroids or catecholamines

• Not recommended in children

• Max dose: 5 mg/kg/hr (83 mcg/kg/min) if >48 hours
Burst-suppression Therapy

Claassen J, et al

• Systematic review of midazolam, pentobarbital, or propofol in terminating seizures and improving outcome in RSE patients

• 28 studies, 193 adult patients (1970-2001)
  - midazolam (n=54), propofol (n=33), pentobarbital (n=106)

• No difference in short term mortality (48%) 
  - Variations in immediate effectiveness and tolerability 
  - Pentobarbital 
    • Lower frequency of short-term treatment failure, breakthrough seizures and changes to a different AED 
    • Higher frequency of hypotension
Burst-suppression Therapy

Rossetti AO, et al

- Prospective, multicenter randomized, unblinded trial to assess effectiveness (RSE control and AE) of propofol vs. barbiturates

- Stopped early due to insufficient recruitment

- Barbiturate group
  - Significantly longer mechanical ventilation (13.5 vs. 4 days)

- No difference with long term outcome and complications
  - Side effects: hypotension, thromboembolic
Burst-suppression Therapy

• Initial duration of 24-48 hours
  - If seizures recur, re-establish

• Over time, duration of cycles is increased

• Overall duration not studied
  - Risk of infection

• Speed of weaning not clear
  - Slowly over days to prevent rebound
Treat with benzodiazepines – for instance IV lorazepam, buccal midazolam, IV or rectal diazepam

Stage 2 - Established Status Epilepticus
Treat with IV antiepileptic drugs – for instance, phenytoin, phenobarbital or valproate

Stage 3 - Refractory Status Epilepticus
Treat with general anaesthesia – for instance, propofol, midazolam, or thiopental/pentobarbital

After 24 hours

Super-refractory Status Epilepticus

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Stage 3: >120 minutes
- Refractory Status Epilepticus
  - Treat with general anaesthesia – for instance, propofol, midazolam, or thiopental/pentobarbital

After 24 hours

Super-refractory Status Epilepticus: Status epilepticus which has continued or recurred despite therapy with general anaesthesia for 24 hours or more

Shorvon S, Ferlisis M. Brain 2011;134:2802-2818
Super-refractory Status Epilepticus

• Exact frequency unknown (~10-15%)
  - The more severe the precipitating insult (trauma, infection, stroke), the more likely SE will become super-refractory

• Causes?
  - Loss of GABAergic receptor density, increase in glutaminergic receptors (NMDA, AMPA receptors)
  - Inflammatory process
    • Opening of blood-brain barrier → excitation
  - Failure to synchronize seizure activity
  - Immunologic, mitochondrial, ID, toxins, genetic diseases

• Establishing cause crucial for treatment
General anaesthesia (including consideration of ketamine), antiepileptic drugs and full intensive treatment unit support; and investigate urgently to identify the cause

- **Cause not identified**
  - IV magnesium bolus 4g; Infusion 2-6g/h (and IV pyridoxine in children 30mg/Kg)
  - Steroids ± IVIG ± plasma exchange
    - Consider hypothermia 32-35°C <48h
    - Consider ketogenic diet (1:1 to 1:4)
    - Consider ECT, CSF drainage and others

- **Cause identified**
  - Treat cause if possible
  - Consider surgery in lesional cases

Shorvon S, Ferlisis M. Brain 2011;134:2802-2818
AED Considerations

• Polytherapy with 2 AEDs
• High dose regimens
• Avoid frequent switching
• Favor AEDs with low interaction potential
• Predictable kinetics
• Lack renal/hepatic toxicity
• Avoid GABAergic drugs
Autoimmune/Inflammatory Etiology

• Greatest influence on the outcome of SE is the underlying cause

• Etiology-specific treatment
  - Encephalitis (example: anti NMDA-receptor)

• No clear guidelines on dose or duration
  - Steroids
  - IVIG
  - Plasmapheresis
  - Rituximab
  - Immunosuppressants
Future Directions

• Lessons from animal models
  - Early treatment of SE may be more effective
  - Early polytherapy may reduce or prevent the development of pharmacoresistance of SE
  - Some drug combinations may have synergistic effects
  - Based upon receptor trafficking in SE, it may be beneficial to enhance inhibition AND reduce excitation very early in the course of treatment
Future Directions

• New antiepileptic drugs: Perampanel
  - AMPA receptors are modified during SE and blockade of AMPA receptors can terminate benzo-refractory SE

• Individualized pharmacological treatment
  - Pharmacogenomics

• Pediatric status epilepticus research group (pSERG)
  - Prospectively obtain pediatric multicenter SE data registry
  - Provide benchmarks and variability of pediatric SE outcomes
  - First step for standardized evaluation and treatment pathways
# Clinical Guidelines

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<td>Acute Gastroenteritis</td>
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<td>Urinary Tract Infection</td>
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Dr. Lindley’s Epilepsy Remedy

- Bromides
- Pleaded guilty to “misbranding”
- “A positive remedy for epilepsy, fits, spasms... if the dose named does not stop at once the attacked and give perfect relief, you should increase the amount until the effect is produced, regardless of the quantity required, and thus, we can assure you, you can do without any danger whatsoever from the medicine”
Thank you!

Questions?

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