Management of refractory status epilepticus in the pediatric population

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Disclosure

**Boards and Editorial work:**
- Laboratory Accreditation Board for Long Term (Epilepsy and ICU) Monitoring (ABRET)
- American Board of Clinical Neurophysiology (ABCN)
- Council member, American Clinical Neurophysiology Society (ACNS)
- Associate Editor, Seizure – European Journal of Epilepsy

**Research Funding:**
- Early Career Physician-Scientist Award, Milken Family Foundation & American Epilepsy Society
- Epilepsy Foundation of America
- Epilepsy Therapy Project
- NIH/NINDS, PPSQ, PPQI, CIMIT, PERC
- Translational Research Program, Children’s Hospital Boston
- Career Development Fellowship, Harvard Medical School and Children’s Hospital Boston
- Investigator initiated research support, Eisai & Lundbeck

**Off label discussions:**
- Off label discussion of multiple status epilepticus treatment options
Learning Objectives

• Provide an overview of symptomatic and etiological treatment options in pediatric patients with refractory status epilepticus.
Outline

• Status Epilepticus Treatment

• Refractory Status Epilepticus Treatment

• Treatment of Etiologies & Comorbidities

• Additional Symptomatic Treatment Options
Status Epilepticus Treatment Algorithm

**First AED:** Lorazepam 0.1 mg/kg iv (Max. 5 mg over 1-4 min)
If no iv: Diazepam 0.3-0.5 mg/kg/dose pr (Max. 20 mg/dose)

Modified after: Boston Children’s Hospital Pharmacy and Therapeutics Committee; Loddenkemper & Goodkin, Curr Treat Options Neurol, 2011
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**Second AED:** Fosphenytoin 20-30 mg PE/kg iv
(If no Fosphenytoin: Phenytoin 20-30 mg/kg iv)
If < 2 years: Consider Pyridoxine 100 mg iv

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**Third AED:** Phenobarbital 20-30 mg/kg iv  
Or: Levetiracetam, valproic acid, and others

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Loddenkemper & Goodkin, Curr Treat Options Neurol, 2011
Distinction from adults

• Immediate initiation of continuous infusion therapy in adults

• Phenobarbital as an intermediate step usually not considered

Riviello et al., Neurocrit Care, 2012
• Status Epilepticus Treatment

• Refractory Status Epilepticus Treatment

• Treatment of Etiologies & Comorbidities

• Additional Symptomatic Treatment Options
Refractory Status Epilepticus

Persistence of SE despite adequate AED therapy:

No response to the standard treatment regimens including adequate dose of first-line and second-line anticonvulsant drugs, such as an initial benzodiazepine followed by another AED.

Bleck, Curr Opin Crit Care, 2005; Brophy et al., Neurocrit Care, 2012
Refractory Status Epilepticus Treatment

First AED: Lorazepam 0.1 mg/kg iv (Max 5 mg over 1-4 min)
If no iv: Diazepam 0.3-0.5 mg/kg/dose pr (Max. 20 mg/dose)

Early/Established Status Epilepticus

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Refractory Status Epilepticus
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**Burst Suppression:** Midazolam 0.2 mg/kg bolus; 0.1-3mg/kg/h
   Or: Pentobarbital 3-5 mg/kg bolus; 0.3-10 mg/kg/h

Modified after: Boston Children’s Hospital Pharmacy and Therapeutics Committee;
Loddenkemper & Goodkin, Curr Treat Options Neurol, 2011
Alternative Symptomatic Treatment Options

- **Midazolam** infusion 0.1 - 3 mg/kg/h after bolus 0.2 mg/kg
- **Pentobarbital** infusion 1-3 mg/kg/h after bolus 10 mg/kg
- **Propofol** infusion 5-10 mg/kg/h after bolus 2 mg/kg
- Isoflurane/Desflurane
- Ketamine
- Paraldehyde
Titration speed & goals (Survey)

- Clinical termination of seizures (34%)
- Electrophysiological seizure termination (63%)
- Burst suppression (69%)

Holtkamp, J Neurol Neursurg Psychiatry, 2003; Riviello et al., Neurocrit Care, 2012
Duration & Weaning

• Most protocols suggest maintaining burst suppression for 24-48 hours

• Prolonged continuation of high-dose therapy may not improve immediate seizure freedom

Sahin et al., Epilepsia, 2001; Riviello et al., Neurocrit Care, 2012
Alternative Symptomatic Treatment Options (intravenous)

- Levetiracetam (20-30 mg/kg load)
- Valproic acid (20-30 mg/kg load)
- Lacosamide
- Lidocaine
Alternative Symptomatic Treatment Options (via NG Tube)

– Topiramate
– Carbamazepine/Oxcarbazepine
– Zonisamide
– Rufinamide
– Other AEDs
• Status Epilepticus Treatment

• Refractory Status Epilepticus Treatment

• Treatment of Etiologies & Comorbidities

• Additional Symptomatic Treatment Options
# Etiology & Comorbidity Treatment

<table>
<thead>
<tr>
<th>ABCs</th>
<th>Hypoxia</th>
<th>Hemodynamics</th>
<th>Hyperthermia</th>
<th>Hypoglycemia</th>
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Hypoxia

- Hypoxia and Hypercarbia
  - ↓ ventilation (chest rigidity from muscle spasm)
  - Hypermetabolism (↑ $O_2$ consumption, ↑ $CO_2$ production)
  - Acidosis

Hypoxia/anoxia markedly increase the risk of mortality in SE

Loddenkemper et al., PLoS One, 2012
Cerebral blood flow - Cerebral O$_2$ requirement

• Hyperdynamic phase
  – CBF meets O2 needs

• Exhaustion phase
  – CBF drops as hypotension sets in
  – Autoregulation exhausted
  – Neuronal damage ensues
Hemodynamics

Sympathetic overdrive
- Massive catecholamine/autonomic discharge
- Hypertension
- Tachycardia

Exhaustion
- Hypotension
- Hypoperfusion

Onset
1 hour
Hyperpyrexia

• Hyperpyrexia may develop during protracted SE, and aggravate possible mismatch of cerebral metabolic requirement and substrate delivery

• Treat hyperpyrexia proactively
  – Antipyretics, external cooling
  – Consider intubation, relaxation, ventilation

Hrncic et al., 2007
Hypothermia

- 25 patients with intractable epilepsy (including 25% children, ages 8-16 years) were treated with extravascular brain hypothermia for several hours & sixty percent had a responder rate of 50% (Sourek et al, 1970).

- 3 children with refractory status epilepticus treated with moderate hypothermia (30°-31°C) (Orlowski et al, 1984).

- 4 adults (ages 54-75 years) with refractory status epilepticus treated with hypothermia (31°-35°C) using an endovascular cooling system. Hypothermia aborted seizure activity in all and 2 patients remained seizure free (Corry et al., 2008).
Hyper- & Hypo-glycemia

- **Hyperdynamic phase**
  - Hyperglycemia

- **Exhaustion phase**
  - Hypoglycemia develops
  - Hypoxia facilitates hypoglycemia
  - Neuronal damage ensues

Graph showing glucose levels over seizure duration with significant decreases noted at 30 min and after SE + hypoxia.
Etiological treatment

**Acute processes**
- Electrolyte disturbance
- CNS infection
- Cerebral Trauma
- Stroke
- Intoxication
- Hypoxic cerebral damage
- Sepsis
- Renal failure

**Chronic processes**
- Pre-existing epilepsy
- Poor AED compliance
- Intracranial space-occupying lesion

Loddenkemper et al., PLoS One, 2012
Etiologies amenable to Immunomodulation

- Rasmussen encephalitis
- Anti-NMDA receptor encephalitis
- Limbic encephalitis
- Hashimoto encephalitis
- Vasculitis
Immunomodulatory Therapies

- Corticosteroids/ACTH
- IVIG
- Plasmapheresis
- Antibodies, i.e. rituximab
- Immunosuppressants, i.e. azathioprine
RE Children’s Project

- Interface with the basic science group order to collect prospectively fluid (serum, CSF) and brain tissue

- Randomized trial of two agents (e.g. IVIG vs. Rituxan) in RE patients.
Refractory Status Epilepticus Surgical treatment algorithm

Continued RSE despite medical management

Lesion on MRI
**Refractory Status Epilepticus Surgical treatment algorithm**

- Continued RSE despite medical management
  - Lesion on MRI
    - Focal lesion present on MRI
      - EEG
        - Concordant
          - Consider resective surgery
**Refractory Status Epilepticus Surgical treatment algorithm**

- **Continued RSE despite medical management**
  - **Lesion on MRI**
    - **Focal lesion present on MRI**
      - **EEG**
        - **Concordant**
          - Consider resective surgery
        - **Not concordant**
          - **Alternative localization information**
    - **No lesion present on MRI**
      - **EEG**
        - **Generalized**
        - **Focal**
Refractory Status Epilepticus Surgical treatment algorithm

Continued RSE despite medical management

Lesion on MRI

Focal lesion present on MRI

EEG

Concordant

Consider resective surgery

Not concordant

Alternative localization information

Generalized

Medical Management/VNS

Focal

Resection

Multifocal

Invasive monitoring/ECoG

No

Yes

Tailored resection

Vendrame & Loddenkemper, Semin Pediatr Neurol, 2010
• Status Epilepticus Treatment

• Refractory Status Epilepticus Treatment

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• Additional Symptomatic Treatment Options
Ketogenic Diet/Modified Atkins Diet

- Two adults with prolonged, nonconvulsive RSE responded to the ketogenic diet with complete seizure control (Wusthof, 2010)

- Two children with nonconvulsive status epilepticus responded to modified Atkins diet (Kumada et al., 2010)

- Propofol infusion syndrome reported in a 10 year old patient after initiation of ketogenic diet (Baumeister, 2004)
Alternative experimental treatment: Brain stimulation

• Vagus Nerve Stimulation
• Transcranial Magnetic Stimulation
• Deep Brain Stimulation
• Electroconvulsive therapy
• Transcranial Direct Current Stimulation
• Functional Transcranial Doppler Ultrasound
Outlook: Individualized pharmacological treatment options

- Pharmacogenetics and pharmacoiresistance (Loddenkemper, Morita & Glauser, 2010)
- Receptor changes during RSE (Loddenkemper et al., unpublished)
- Medication selection based on neurophysiological recordings (Sun, unpublished)
Receptor Changes in Human Tissue during RSE

- NMDAR expression was altered to the greatest extent in tissue removed during acute RSE.

- Tissue from patients with ESES demonstrated the most prominent alterations in AMPARs.

- Altered GABARα subunit expression was more evident in tissue from patients with chronic epilepsy, as has been previously reported.

Loddenkemper et al., unpublished
Outlook

• Mechanistic synergy of existing drugs
• New drugs
• Implantable drug delivery devices
• Stem cell therapy
• Altered Gene Expression
• Prevention
• Multicenter trials
Outlook: Multicenter Trials
Pediatric Status Epilepticus Research Group (pSERG): 57 patients enrolled

<table>
<thead>
<tr>
<th>Sites</th>
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<th>Site Principal Investigator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Children’s Hospital</td>
<td>Boston</td>
<td>Iván Sánchez Fernández, Tobias Loddenkemper</td>
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<tr>
<td>Children’s Hospital of Philadelphia</td>
<td>Philadelphia</td>
<td>Nicolas Abend</td>
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<tr>
<td>Cincinnati Children’s Hospital</td>
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<td>Tracy Glauser, Ravi Arya &amp; Katrina Peariso</td>
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<td>Colorado Children’s Hospital</td>
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<td>Duke University Medical Center</td>
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If everything else fails…
Thank you