Refractory Status Epilepticus in Children: What are the Options?

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Objectives

1. Describe the initial therapeutic management of status epilepticus in pediatrics.

1. Analyze current literature surrounding the use of available therapies for refractory status epileptics in pediatrics.
Definitions

**Brief Seizure**

< 5 minutes

**Prolonged Seizure**

5 – 30 minutes

**Status Epilepticus**

> 30 minutes of continuous epileptic seizure activity
Recurrent seizure activity without recovery between seizures

**Refractory Status Epilepticus**

*Persistence of clinical or electrographic seizures after benzodiazepine + ONE antiepileptic drug (AED)*

Epidemiology

Status Epilepticus (SE)

- Most common neurological emergency in childhood
- Incidence between 17-23 per 100,000 children per year

Common Etiologies

**Neonates:**
- Encephalopathy
- Infection
- Stroke/Hemorrhage
- Congenital Malformation
- Metabolic Disturbances

**Children:**
- Infection
- Fever
- Congenital Malformation
- Metabolic Disturbances

2016 American Epilepsy Society
Convulsive Status Epilepticus

0 - 5 minutes
Stabilization Phase
- Stabilize patient, vital signs, provide oxygenation, initial ECG, check blood glucose, attempt IV access, collect electrolytes

5 - 20 minutes
Initial Therapy Phase
- First line: IM midazolam, IV lorazepam, IV diazepam
- Second line: IV phenobarbital, rectal diazepam, intranasal midazolam, buccal midazolam

20 - 40 minutes
Second Therapy Phase
- Choose 1 and give as a single dose: IV fosphenytoin, IV valproic acid, IV levetiracetam
- If the above is unavailable, give IV phenobarbital

40 - 60 minutes
Third Therapy Phase
- No clear evidence to guide therapy: repeat second line or anesthetic doses of midazolam, pentobarbital, or propofol with continuous EEG monitoring

30% of patients with SE will fail conventional therapy and progress into refractory status epilepticus

Internalization of \( \text{GABA}_A \) Receptors

Consequences of RSE

Metabolic acidosis
Cerebral necrosis
Hypoxia
Hyper/Hypoglycemia
Increased Intracranial Pressure
Respiratory acidosis
Leukocytosis
Tachycardia
Hyperpyrexia
Hyper/Hypotension

Morbidity and Mortality

• In a series of 193 children with refractory SE, 26% had seizures lasting longer than 1 hour
  – Neurologic sequelae:
    • 29% of infants < 1 year
    • 11% of children 1-3 years
    • 6% of children > 3 years

• Children with SE have an overall mortality rate of 0-3%

  *In a retrospective series of 22 children with refractory SE, mortality was 32%*

Goals of Therapy

- Achieve burst suppression to induce a therapeutic coma
- Recommend to continue anesthetic infusion for 24-48 hours after seizures are terminated, then gradually discontinue

What are the Options in Pediatrics?

- Pentobarbital
- Midazolam
- Propofol
- Ketamine
- Topiramate
- Lidocaine
- Lacosamide
- Levetiracetam
- Valproic Acid
Mechanism of Action for GABAnergic Agents

# Continuous Infusion of Pentobarbital


<table>
<thead>
<tr>
<th>Population</th>
<th>30 patients (mean age: 6.5 years, range: 0.03-18.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>Loading Dose: 5.4 mg + 2.8 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion: $1.1 \pm 0.4$ mg/kg/hour (range: 0.3 – 2)</td>
</tr>
<tr>
<td></td>
<td>Mean duration: $166 \pm 112$ hours (6.9 days)</td>
</tr>
<tr>
<td><strong>Neurologic Outcome</strong></td>
<td>Mean time to achieve burst suppression: $22.6 \pm 17.5$ hours</td>
</tr>
<tr>
<td></td>
<td>Sustain burst suppression without relapse: 33% (n=10)</td>
</tr>
<tr>
<td><strong>Therapy Tolerance</strong></td>
<td>Hemodynamic support: 93.3% (n=28)</td>
</tr>
<tr>
<td></td>
<td>Acquired infections: 66% (n=20)</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis: 10% (n=3)</td>
</tr>
<tr>
<td></td>
<td>Metabolic acidosis: 10% (n=3)</td>
</tr>
<tr>
<td><strong>Negative Outcome</strong></td>
<td>Death: 3 patients (10%)</td>
</tr>
<tr>
<td></td>
<td>Children &lt; 5 years experienced more negative outcomes (62%)</td>
</tr>
</tbody>
</table>

## Continuous Infusion of High-dose Midazolam

**Morrison, et al. 2006.**

<table>
<thead>
<tr>
<th>Table Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>17 patients (mean age: 4.7 years)</td>
</tr>
<tr>
<td>Neurologic Outcomes</td>
<td>15 patients (88%) controlled in mean of 15 minutes with midazolam</td>
</tr>
</tbody>
</table>
| Therapy Tolerance          | Median peak rate for seizure control was 0.24 mg/kg/hr  
Mean arterial BP was 67 ± 19 mmHg *prior to therapy*  
Mean arterial BP was 65 ± 10 mmHg at *peak of infusion* (*p = 0.6*)                                                                 |
| Negative Outcome           | Breakthrough seizures occurred in 8 episodes (47%)  
2 patients failed to achieve seizure control  
3 patients expired due to underlying acute neurological pathology                                                             |
Continuous Infusion of High-dose Midazolam

RSE
- Bolus 0.5 mg/kg
- Infusion 2 mcg/kg/min (0.12 mg/kg/hr)

5 min
- Bolus 0.5 mg/kg
- Increase infusion to 4 mcg/kg/min (0.24 mg/kg/hr)

5 min
- Bolus 0.1 mg/kg
- Increase infusion by 4 mcg/kg/min (0.48 mg/kg/hr)
  - Repeat PRN to attainment of 24 mcg/kg/min (1.44 mg/kg/hr)

5 min
- Initiate thiopental
  Bolus 4 mg/kg + Infusion 2 mg/kg/hr

## Propofol/Thiopental

<table>
<thead>
<tr>
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<th>Propofol</th>
<th>Thiopental</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>Bolus: 1-2 mg/kg</td>
<td>Loading dose: blood level of 20 mg/mL after 6 hours, then continuous infusion</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion: 1-2 mg/kg/hour</td>
<td></td>
</tr>
<tr>
<td><strong>Episodes of RSE</strong></td>
<td><strong>22</strong></td>
<td><strong>20</strong></td>
</tr>
<tr>
<td><strong>Seizure cessation</strong></td>
<td><strong>14/22 (64%)</strong></td>
<td><strong>11/2- (55%)</strong></td>
</tr>
<tr>
<td><strong>Mean duration</strong></td>
<td><strong>2.3 (0.4-11) days</strong></td>
<td><strong>8.6 (2 – 33) days</strong></td>
</tr>
<tr>
<td><strong>(range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td><strong>2 (not related to propofol)</strong></td>
<td><strong>2 (related to thiopental)</strong></td>
</tr>
</tbody>
</table>

Mobilization of NDMA and AMPA Receptors

Synaptic membrane
Mechanism of Action for Ketamine

**Potentiation of GABA**

Image from: http://pedsinreview.aappublications.org/content/19/10/342

<table>
<thead>
<tr>
<th></th>
<th>Pentobarbital (n = 630)</th>
<th>Pentobarbital and Ketamine (n = 48)</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>3 (0-10)</td>
<td>7 (2-11)</td>
</tr>
<tr>
<td><strong>Treatment Details</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First day of pentobarbital</td>
<td>2 (1-4)</td>
<td>2 (0-4)</td>
</tr>
<tr>
<td>Days of pentobarbital</td>
<td>5 (3-9)</td>
<td>14 (8-30)</td>
</tr>
<tr>
<td>First day of ketamine</td>
<td>--</td>
<td>11 (5-20)</td>
</tr>
<tr>
<td>Days of ketamine</td>
<td>--</td>
<td>7 (4-9)</td>
</tr>
<tr>
<td>Any midazolam treatment</td>
<td>610 (97%)</td>
<td>47 (98%)</td>
</tr>
<tr>
<td>First day of midazolam</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Days of midazolam</td>
<td>6 (3-12)</td>
<td>16 (7-32)</td>
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Median (IQR)


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<td>Days of pentobarbital</td>
<td>5 (3-9)</td>
<td>14 (8-30)</td>
</tr>
<tr>
<td>First day of ketamine</td>
<td>--</td>
<td>11 (5-20)</td>
</tr>
<tr>
<td>Days of ketamine</td>
<td>--</td>
<td>7 (4-9)</td>
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<tr>
<td>EEG days*</td>
<td>10 (6-12)</td>
<td>24 (17-43)</td>
</tr>
<tr>
<td>Pressor days*</td>
<td>4 (1-8)</td>
<td>8 (4-15)</td>
</tr>
<tr>
<td>Ventilator days*</td>
<td>14 (9-23)</td>
<td>30 (20-56)</td>
</tr>
<tr>
<td>ICU days*</td>
<td>17 (9-28)</td>
<td>29 (20-56)</td>
</tr>
<tr>
<td>Length of stay*</td>
<td>30 (18-52)</td>
<td>51 (30-93)</td>
</tr>
<tr>
<td>Died in Hospital*</td>
<td>108 (17%)</td>
<td>14 (29%)</td>
</tr>
</tbody>
</table>

Note: *p value << 0.001
Median (IQR)
Mechanism of Action for Lacosamide

Potentiation of GABA

Antagonize AMPA receptors

Inhibits repetitive neuronal firing by enhancing the slow inactivation of sodium channels
Lacosamide for Status Epilepticus

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<tr>
<td><strong>Objective</strong></td>
</tr>
<tr>
<td><strong>Method</strong></td>
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</table>
| **Result**            | Nine children (mean age: 5.7 years)  
                        | Mean Loading dose: 8.7 mg/kg (3.3 – 10 mg/kg)  
                        | Efficacious: 7 out of 9 patients (77.8%)  
                        | Seizure free: 4 out of 9 patients (44.4%) |
| **Conclusion**        | Appropriate adjunctive therapy  
                        | Loading dose 10 mg/kg  
                        | Total daily dose: 15-20 mg/kg |

## Topiramate (TPM)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Type</th>
<th>Age</th>
<th>No. of ADEs Prior to TPM</th>
<th>Dosage</th>
<th>Time to TPM respond</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahriman M, et al. 2003</td>
<td>Case series (n=3)</td>
<td>4.5 months – 11 years</td>
<td>2-6</td>
<td>2-3 mg/kg/day (max: 5-6 mg/kg/day)</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Blumkin L, et al. 2005</td>
<td>Case series (n=2)</td>
<td>5-32 months</td>
<td>3-7</td>
<td>2-5 mg/kg, then 22-25 mg/kg/day, maintenance 10 mg/kg/day</td>
<td>6 days</td>
</tr>
<tr>
<td>Perry MS, et al. 2006</td>
<td>Case series (n=3)</td>
<td>2 months – 6 years</td>
<td>2</td>
<td>10 mg/kg/day x 2 days, then 5 mg/kg/day</td>
<td>12-21 hours</td>
</tr>
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<tbody>
<tr>
<td>Bragatti JA, et al. 2011</td>
<td>Case report (n=1)</td>
<td>16 years</td>
<td>1</td>
<td>2.5 mg/kg/day</td>
<td>8 hours</td>
</tr>
<tr>
<td>Akyildiz BN, et al. 2011</td>
<td>Prospective observational (n=14)</td>
<td>6 months - 12 years</td>
<td>0-2</td>
<td>5 mg/kg loading dose, then 5 mg/kg/day</td>
<td>2-48 hours</td>
</tr>
<tr>
<td>Shelton CM, et al. 2014</td>
<td>Case series (n=1)</td>
<td>12 years</td>
<td>3</td>
<td>Initial 1.7 mg/kg/day, titrate to 11.4 mg/kg/day</td>
<td>72 hours</td>
</tr>
</tbody>
</table>
Treatment plan: RSE

Refractory Status Epilepticus

Midazolam
Pentobarbital

Propofol in adult

Use of propofol in children is not recommended

Ketamine
Topiramate
Valproic acid
Levetiracetam
Lacosamide
Summary

• Status epilepticus is the most common neurological emergency of childhood.

• **Refractory status epilepticus** is associated with a mortality rate of 32%.

• Treatment strategies and preferences for refractory status epilepticus are not well established.
  – Benzodiazepines and Pentobarbital remain the main cornerstone of treatment
Questions?
Refractory Status Epilepticus in Children: What are the Options?

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