Seize the moment: Management of status epilepticus in adults and children

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Presentor Disclosures

• Laura Wang
  • I have no current or past relationships with commercial entities
  • I have received no speaker’s fee for this learning activity

• Sharon Yamashita
  • I have no current or past relationships with commercial entities
  • I have received no speaker’s fee for this learning activity
Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization
Learning Objectives

• At the conclusion of this presentation, participants will be able to:
  • Define status epilepticus
  • Describe the epidemiology, pathogenesis, goals of therapy of status epilepticus in both adults and children
  • Recognize the evolution of status epilepticus over time and implications on pharmacotherapy
  • Understand the rationale for guideline recommendations on the management of status epilepticus in adults and children
  • Explore therapeutic options for the management of refractory status epilepticus
Outline

• Status Epilepticus
  • Definition, Epidemiology, Pathogenesis, Goals of Therapy

• Management in Adults
  • Guidelines and landmark trials
  • Firstline therapy
  • Refractory status epilepticus

• Management in Children
  • Guidelines and landmark trials
  • Febrile seizures
  • Neonatal seizures

• Prognosis/Outcomes
Definition

“….a 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 t1)......that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks.....”

<table>
<thead>
<tr>
<th>Type of SE</th>
<th>Operational dimension 1</th>
<th>Operational dimension 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (t₁), when a seizure is likely to be prolonged leading to continuous seizure activity</td>
<td>Time (t₂), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)</td>
</tr>
<tr>
<td>Tonic-clonic SE</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 epilepticus</td>
<td>10–15 min⁴</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

ILAE Taskforce 2015
Epidemiology

- Incidence of 12.6 cases/100,000 person years → most common neurological emergency
- 1/3 of SE cases are the initial presentation of a seizure disorder
- 1/3 occur in patients with established epilepsy diagnosis
  - 0.5-6.6% occurrence of SE in diagnosed epileptics
- 1/3 occur as result of acute isolated brain insult

Etiology in children

- **Remote symptomatic epilepsy** (34%)
  - CNS malformation, previous TBI, chromosomal disorder
- **Acute symptomatic seizures** (26%)
  - CNS infection 13%
  - Acute metabolic disorder 6%
  - Other: electrolyte disturbance, sepsis, hypoxia, trauma
- **Febrile** excluding CNS infections (22%)
  - URTI, sinusitis, sepsis
- Cryptogenic 15%
- Progressive encephalopathy 3%
  - Mitochondrial disorders, CNS lipid storage disease, organic acidopathies

Neurology 2006;67:1542
Etiology in adults

- Cerebrovascular accident (ischemic stroke, intracerebral hemorrhage)
- Low antiseizure drug levels (noncompliance, drug interaction)
- Remote brain pathology (e.g. trauma, stroke, cortical dysplasia)
- Head trauma
- Infection
- Hypoxic brain injury
- Posterior reversible encephalopathy syndrome (PRES)
- Autoimmune and paraneoplastic etiologies
- Metabolic disturbances (electrolyte abnormalities, hypoglycemia)
- Drug withdrawal, toxicity
From seizure to status epilepticus

Stage 1: Milliseconds-seconds
- Protein phosphorylation
- Ion channel opening and closing
- Neurotransmitter release

Stage 2: Seconds-minutes
- Receptor trafficking
  - Decrease in inhibitory GABA_A β2/β3 and γ2 subunits
  - Increase in excitatory NMDA receptors
  - Increase in excitatory AMPA receptors

Stage 3: Minutes-hours
- Neuropeptide expression
  - Increase in excitatory substance P
  - Insufficient replacement of inhibitory neuropeptide Y

Stage 4: Days-weeks
- Genetic and epigenetic changes
  - Gene expression
  - DNA methylation
  - Regulation of microRNA

Clinical time course of status epilepticus

Continuum (Minneap Minn) 2013;19(3):767–794
Goals of therapy

• Stop the seizure at the earliest timepoint and prevent recurrence
• Prevent progression to refractory status epilepticus (RSE)
• Identify and treat the underlying etiology
• Support ABCs (airway breathing circulation) + normoglycemia
• Anticipate and minimize adverse effects of therapy
Management of Status Epilepticus in Adults
Getting Started…

• Airway, Breathing, Circulation
• Rule out reversible causes:
  • Hypoglycemia
    ➢ thiamine/glucose (D50W)
• Antiepileptics
  • Abort seizure
  • Prevent further seizures

• Labwork
  • Hypo/Hypernatremia
  • Renal Failure
• Consider drug-induced/drug-withdrawal
• Brain Imaging
  • CT/CTA/MRI
• Diagnostic Procedures
  • lumbar puncture
• EEG
Polling Question

• Which of the following medications would be LEAST appropriate for the initial management (first 5 minutes) of a patient with status epilepticus?

A. IV lorazepam
B. IM midazolam
C. IV phenytoin
D. IV phenobarbital
Figure 3: Updated treatment algorithm for generalised convulsive status epilepticus in adults and older children. PE—phenytoin equivalents.
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 D25SW IV
   - Children < 2 years: 4 ml/kg D12.5W
6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels

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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)

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If patient at baseline, then symptomatic medical care

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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)

---

If patient at baseline, then symptomatic medical care

---

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

---

If patient at baseline, then symptomatic medical care

---

FIGURE 1. Proposed treatment algorithm for status epilepticus.
The First 5 - 10 Minutes
The First 5 - 10 minutes...
Benzodiazepines to stop the seizures

Lorazepam
2–4 mg intravenous (2 mg/min)
(repeat if needed)
or
Midazolam
10 mg intramuscular (repeat if needed)

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)

Epilepsy Currents, 2016; 16: 48–61

Lancet Neurol 2015; 14: 615-24
Veterans Affairs Status Epilepticus Study

- Seizures > 10 min
- Double-blind, randomized:
  - IV lorazepam (n= 136)
    - 0.1 mg/kg
  - IV phenobarbital (n=124)
    - 15 mg/kg
  - IV diazepam and IV phenytoin (n= 131)
    - 0.15 mg/kg and 18 mg/kg
  - IV phenytoin (n=127)
    - 18 mg/kg

Successful treatment:
No clinical/electrical seizures within 20 minutes and no recurrence from 20 – 60 minutes
The RAMPART Trial
NEJM 2012; 366: 591-600

• Pre-hospital (seizures > 5 min)
• Double-blind, randomized, noninferiority trial:
  • IM midazolam 10 mg (n=448)
  • IV lorazepam 4 mg (n=445)

<table>
<thead>
<tr>
<th>Outcome (ITT)</th>
<th>IM Midazolam (n=448)</th>
<th>IV Lorazepam (n=445)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Termination of seizures (%)</td>
<td>73.4 (69.3 – 77.5)</td>
<td>63.4 (58.9 – 67.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rescue therapy administered</td>
<td>22 (4.9)</td>
<td>42 (9.4)</td>
<td></td>
</tr>
</tbody>
</table>

ITT - intention to treat, CI – confidence intervals
Within 30 minutes
Polling Question

• After initial therapy is started, which of the following medications would be LEAST appropriate to manage ongoing seizures?

A. Lorazepam 2 mg q6h IV
B. Levetiracetam 60 mg/kg IV
C. Phenytoin 20 mg/kg IV
D. Phenobarbital 15 mg/kg IV
Within 30 minutes...
Anticonvulsants to prevent ongoing seizures

Phenytoin
- 20 mg/kg intravenous (50 mg/min)
  or
Fosphenytoin
- 20 mg/kg PE intravenous (150 mg/min)
  (can give additional 5–10 mg/kg of either)

Valproic acid
- 20–30 mg/kg intravenous (about 100 mg/min)
  or
Phenobarbital
- 20 mg/kg intravenous (50–75 mg/min)
  or
Levetiracetam
- 20–60 mg/kg (more than 15 min)

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, single dose, Level B)

Epilepsy Currents, 2016; 16: 48–61
The ESETT Trial  
NEJM 2019; 381: 2103-13

• Seizures > 10 min  
  • 5 min after receiving BZD
• Randomized, blinded, adaptive trial:
  • IV levetiracetam (n= 145)
    • 60 mg/kg
  • IV fosphenytoin (n= 118)
    • 20 mg/kg PE
  • IV valproate (n= 121)
    • 40 mg/kg

BZD = benzodiazepine, PE = phenytoin equivalents
# Choice of Anticonvulsant

<table>
<thead>
<tr>
<th></th>
<th>Phenytoin</th>
<th>Fosphenytoin</th>
<th>Phenobarbital</th>
<th>Valproic Acid</th>
<th>Levetiracetam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Term</strong></td>
<td>Hypotension, arrhythmias, vesicant, nystagmus</td>
<td>Pruritus, burning, parasthesias, nystagmus</td>
<td>Hypotension, respiratory depression, prolonged sedation</td>
<td>Injection site reactions</td>
<td>Well tolerated</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td></td>
<td>Less hypotension, arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Considerations</strong></td>
<td>Max rate 50 mg/min (~30 min)</td>
<td><strong>Max rate 150 mg/min</strong> (PE); can be given IM (~10 min)</td>
<td></td>
<td>IV – Special Access in Canada</td>
<td></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$180 (1.5g)</td>
<td>$ 200 (1.5g)</td>
<td>$200 (1.6g)</td>
<td></td>
<td>$135 (3g)</td>
</tr>
</tbody>
</table>

*McKesson September 2022

PE = phenytoin equivalents
After 30 minutes
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, pentobarbital, or propofol (all with continuous EEG monitoring)

Thiopental – no longer available in Canada, Pentobarbital – Special Access in Canada
After 30 minutes...

**Titrate to burst suppression on EEG**

<table>
<thead>
<tr>
<th>DRUG (OFF-LABEL USE)</th>
<th>USUAL DOSE</th>
<th>MAX DOSE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIDAZOLAM</td>
<td>0.3 – 20 mg/h</td>
<td>3 mg/kg/h</td>
<td>Risk of accumulation with high doses/prolonged use</td>
</tr>
<tr>
<td>PROPOFOL</td>
<td>20 – 100 mcg/kg/min</td>
<td>200 mcg/kg/min</td>
<td>Risk of propofol infusion syndrome with doses &gt; 80 mcg/kg/min &gt; 48 hours</td>
</tr>
<tr>
<td>KETAMINE</td>
<td>0.1 – 4 mg/kg/h</td>
<td>10 - 15 mg/kg/h</td>
<td>Less likely to cause hypotension</td>
</tr>
<tr>
<td>ISOFLURANE</td>
<td>2 – 5 mL/h</td>
<td></td>
<td>Contraindicated if history of malignant hyperthermia, raised intracranial pressure</td>
</tr>
</tbody>
</table>
Maintenance Therapy

- Phenytoin
- Levetiracetam
- Lacosamide
- Valproic Acid
- Phenobarbital
- Clobazam
- Lamotrigine
- Carbamazepine
- Topiramate
- Perampanel
Refractory Status Epilepticus

• Persistant seizures despite 2 antiepileptic drugs
  • 20 – 30% of patients with status epilepticus
  • “NORSE” – new onset
  • “Super-Refractory” - > 24h despite extensive antiseizure therapy

• Management
  • Anaesthetic doses of midazolam, propofol, ketamine
  • General Anaesthetic (isoflurane, sevoflurane)
  • Multiple antiepileptics as maintenance therapy
  • Immunotherapy (encephalitis): corticosteroids, IV immune globulin, plasmapheresis
  • IV magnesium, hypothermia, ketogenic diet
Volatile General Anaesthetics – isoflurane/sevoflurane

ADVANTAGES

• rapid and easy titration
  • Can turn off for EEG
• Minimal hemodynamic effects (low dose)
• Not renally/hepatically cleared
• Low systemic accumulation

DISADVANTAGES

• Feasibility limited by delivery system/scavenging devices
  • Anaesthetic Conserving Device
    • Small miniature vaporizer which can be connected to an ICU ventilator
  • Also use scavenging devices to reduce environmental emissions
• Side effects: risk of malignant hyperthermia, accumulation of fluoride, withdrawal seizures?
Isoflurane in (Super) Refractory Status Epilepticus Neurocrit Care 2021; 35:631–639

- Multi-centre, retrospective
- n=45 (2011-18)
  - 12 refractory
  - 33 super refractory
- Median # antiepileptics 5 (2-10)
- Median onset day 5 (0-58)

- Burst suppression 71%
- Termination of seizures
  - 29% isoflurane alone
  - 50% isoflurane + additional tx
- Adverse effects:
  - 80% Hypotension
  - 44% Infection
## Therapies for Refractory Status Epilepticus


<table>
<thead>
<tr>
<th>DRUG</th>
<th>NUMBER OF PATIENTS</th>
<th>TERMINATION OF STATUS EPILEPTICUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIDAZOLAM</td>
<td>585</td>
<td>78%</td>
</tr>
<tr>
<td>PROPOFOL</td>
<td>143</td>
<td>68%</td>
</tr>
<tr>
<td>PENTOBARBITAL/THIOPENTAL</td>
<td>192</td>
<td>64%</td>
</tr>
<tr>
<td>KETAMINE</td>
<td>68</td>
<td>63%</td>
</tr>
<tr>
<td>ISOFLURANE</td>
<td>45</td>
<td>29-51%</td>
</tr>
</tbody>
</table>
Drug-induced seizures

• ~9% of status epilepticus cases
• Symptoms are similar to non-drug induced SE
• Common culprits:
  • Antidepressants
  • Stimulants
  • Antipsychotics
  • Antihistamines
  • Anticancer drugs
  • Hypoglycemic agents
  • Immunosuppressants
  • Antimicrobials
  • Pulmonary drugs (aminophylline, theophylline)
• AVOID phenytoin
  Shown to be ineffective, and may be harmful in lidocaine, theophylline and TCA induced seizures

1st line agents:
Benzodiazepines
Pyridoxine if suspected isoniazid overdose

2nd line agent:
IV Phenobarbital
Propofol
AVOID phenytoin

3rd line agent:
Midazolam continuous infusion
Propofol infusion
Pentobarbital/thiopental

Other therapies:
Ketamine
Levetiracetam
GI decontamination, hemodialysis, antidote
Management of Status Epilepticus in Children
1st line - what does the literature say?

• PECARN study
  • Double-blinded multicentre RCT of 273 children aged 3 mos – 18 years
  • Randomized 1:1 to IV diazepam 0.2 mg/kg (max 8 mg) or IV lorazepam 0.1 mg/kg (max 4 mg), with the option to repeat half of the initial dose if seizures persisted after 5 mins
  • No difference between IV diazepam (72.1%) and IV lorazepam (72.9%) in termination of SE by 10 min, without recurrence within 30 min
  • 16%-17% incidence of respiratory depression requiring assisted ventilation in both groups

JAMA. 2014;311(16):1652–60
1st line - what does the literature say?

• RAMPART (analysis of pediatric cohort)
  • 120 children randomized 1:1 to receive IV lorazepam or IM midazolam
  • For primary outcome of seizure cessation before reaching ED, no significantly
difference between IV lorazepam (71.6%) group vs IM midazolam (68.3%) group
  • For secondary endpoints: rates of hospital and ICU admission, endotracheal intubation, and recurrent seizure, point estimates are all favorable for IM midazolam
1st line – what does the literature say?

- A network meta-analysis\(^1\) of 16 RCTs including 1821 patients compared the efficacy of midazolam, lorazepam, and diazepam in treating pediatric SE
  - Non-IV midazolam and IV lorazepam were more efficacious than diazepam
  - IV lorazepam was noninferior to non-IV midazolam
  - Intramuscular midazolam most efficacious non-IV medication
  - Intranasal midazolam most efficacious non-IV medication for achieving seizure cessation within 10 mins, and for non-recurrence within 1hr
  - Very limited evidence for sublingual/buccal lorazepam use; one study shows it is even less effective than rectal diazepam (56% vs 79%)

\(^1\)J Child Neurol. 2016;31(9):1093–107
Putting it to practice

- **Prehospital:**
  - IM/Buccal/IN midazolam → preferred choice in children without IV access
  - Buccal lorazepam → easiest, but of lowest efficacy
  - PR diazepam → slowest onset, variable absorption, ?socially acceptable

- **In hospital:**
  - With IV access:
    - IV lorazepam or IV/IM midazolam have similar efficacy
  - Without IV access:
    - Buccal, IN, IM midazolam is drug of choice

- Treating with more than 2 doses of benzodiazepines associated with increased risk for respiratory depression and decreased efficacy
Benzodiazepines – 1\textsuperscript{st} line therapy

• Adverse effects and management
  • Sedation, respiratory depression, hypotension
  • Rare at appropriate dosing and at <2 doses
  • Paradoxical reaction (1-10% incidence?)
    • Transient sedation followed by extreme agitation, aggression, hyperactivity, hallucination
    • May be due to genetically mediated alterations in GABA binding sites
    • May react paradoxically to one benzodiazepine but not others
    • Requires more research
<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam IV/IO</td>
<td>0.1 mg/kg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Midazolam IM/IN</td>
<td>0.2 mg/kg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Midazolam buccal</td>
<td>0.5 mg/kg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Lorazepam IV/IO</td>
<td>0.05-0.1 mg/kg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Diazepam IV/IO</td>
<td>0.3 mg/kg</td>
<td>5 mg (&lt;5 yr) 10 mg (&gt;= 5 yrs)</td>
</tr>
<tr>
<td>Diazepam PR</td>
<td>0.5 mg/kg</td>
<td>20 mg</td>
</tr>
</tbody>
</table>
2\textsuperscript{nd} line – what does the literature say?

- **ConSEPT**
  - Open-label, multicentre RCT in Australia and New Zealand
  - Enrolled 244 children 1:1 to receive IV LEV 40 mg/kg or IV PHT 20 mg/kg
  - LEV NOT superior to PHT for seizure cessation after 5 min (60% vs 50%)

- **EcLipSE**
  - Open-label, multicentre RCT in UK
  - Enrolled 286 children 1:1 to receive IV LEV 40 mg/kg vs IV PHT 20 mg/kg
  - No difference between LEV or PHT for seizure termination (70% vs 64%)

- **ESETT**
  - Enrolled 225 children >2 yo
  - No differences in efficacy between IV LEV 60 mg/kg, IV VPA 40 mg/kg, IV FosPHT 20 mg/kg
  - IV LEV is the safest option
## ESETT – secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Levetiracetam</th>
<th>Fosphenytoin</th>
<th>Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>85</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>53 (62%)</td>
<td>45 (63%)</td>
<td>43 (62%)</td>
</tr>
<tr>
<td>Length of ICU stay, days</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Safety population</td>
<td>86</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Life-threatening hypotension</td>
<td>0</td>
<td>2 (3%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>within 60 min of start of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>drug infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening cardiac arrhythmia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>within 60 min of start of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>drug infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute respiratory depression</td>
<td>5 (6%)</td>
<td>13 (18%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>7 (8%)</td>
<td>24 (33%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>within 60 min of start of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>drug infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute seizure recurrence</td>
<td>8 (9%)</td>
<td>11 (15%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>60 min-12 h after start of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>drug infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
### 2nd line treatment in children

If <18 months, consider a dose of pyridoxine 100 mg IV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam IV (avoid or adjust dose in severe renal impairment)</td>
<td>60 mg/kg (max 4500 mg/dose), diluted in NS or D5W to final concentration of 15-50 mg/mL and given over 5-15 min.</td>
</tr>
<tr>
<td>OR Fosphenytoin IM or IV (contraindicated in drug-induced seizures)</td>
<td>20 mg phenytoin equivalents (PE)/kg (max 1500 mg PE/dose); if using IV give in NS or D5W over 5-10 min; max volume per IM site: 3 mL. (If child &gt;30 kg, IM dosing may not be practical because of large volume requiring multiple IM sites)</td>
</tr>
<tr>
<td>OR Phenytoin IV (use if fosphenytoin not available; contraindicated in drug-induced seizures)</td>
<td>20 mg phenytoin equivalents (PE)/kg (max 1500 mg PE/dose) in NS only over 20-30 min</td>
</tr>
<tr>
<td>OR Phenobarbital IV (preferred for refractory febrile seizures in &lt;6 mo or drug-induced seizures)</td>
<td>20 mg/kg undiluted over 5-10 min (max: 1000 mg/dose); MD must be present to monitor for cardiorespiratory depression</td>
</tr>
<tr>
<td>OR Valproic Acid IV (available only through SAP)</td>
<td>30 mg/kg in NS over 5 min, followed by 10 mg/kg if ineffective after 10 min</td>
</tr>
</tbody>
</table>
Pathogenesis of febrile seizure

Infection (often HHV6 or influenza virus) in Child (typically age 6 mo-6 years)

- Synthesis of IL-1β in hippocampus
- Fever ≥38°C
- Exogenously elevated brain temperature (i.e. hot bath)

GABA_A receptor subunit mutation
Sodium channel subunit mutation
Increased production of fever mediators (IL-1β)

Physiologic Conditions

- Elevated temperature impacts ion channels
- ↑ glutamate and/or ↓ GABA
- ↑ excitability and synchronization of activity

Familial or Sporadic Genetic Susceptibility to Elevated Temperature

Febrile Seizure

Adapted from Calgary Guide
Febrile status epilepticus

• FEBSTAT
  • Multicentre prospective observational study of FSE treatment and outcomes
  • Enrolled 199 patients between 4 months – 6 years old
  • FSE stopped spontaneously in only 20 children (10%)
  • 140 (78%) required more than one medication before FSE termination
    • Most received a benzodiazepine
    • Almost 40% of benzodiazepine doses were inadequate
  • Median time from the seizure onset to first medication was 30 min
  • FSE proved difficult to terminate, even with medication administration
  • Earlier onset of treatment results in shorter total seizure duration
  • No clear evidence that barbiturate coma or midazolam infusion was better than IV fosphenytoin or IV phenobarbital after initial benzodiazepine failure
Refractory status epilepticus in children

• Multivariate analysis showed that patients who received untimely first-line benzodiazepine treatment had:
  • higher odds of death (adjusted odds ratio 11.0; 95% CI, 1.43 to ∞; \(P = .02\))
  • greater odds of receiving continuous infusion (AOR, 1.8; 95% CI, 1.01-3.36; \(P = .047\))
  • longer convulsive seizure duration (AOR, 2.6; 95% CI, 1.38-4.88; \(P = .003\))
  • more frequent hypotension (AOR 2.3; 95% CI, 1.16-4.63; \(P = .02\))
Neonatal seizures

• Neonatal brains are immature, with excitatory (glutaminergic) pathways predominating inhibitory (GABAergic) pathways
• Inborn errors of metabolism and congenital brain malformations first declare themselves in perinatal period
• Incidence of seizures in the neonatal period is high, estimated at 1-5/1000 live term births
• Pharmacotherapy focuses on GABAergic stimulation
Neonatal seizure pharmacotherapy

• Phenobarbital → Considered first line
  • RCT data; most clinical/historical experience
  • Complete cessation of seizures in 40-50%
  • 80% reduction in seizure frequency in 80%

• Levetiracetam → 2nd line
  • Retrospective data; lacking clinical experience (relatively new)
  • 88% seizure free in one study of 23 neonates
  • 100% seizure free in 72h in another study of 22 neonates

• Phenytoin → alternative 2nd line
  • RCT data showing 45-60% complete cessation
  • Unpredictable metabolism and enteral absorption in neonates

Neonatal seizure guidelines. Hospital for Sick Children.

Seizures ongoing for 2 minutes

Lorazepam 0.1 mg/kg IV/PR
Administer over 2 minutes

Seizures 2 minutes after the completion of infusion

Lorazepam 0.1 mg/kg IV/PR
Administer over 2 minutes

Seizures 2 minutes after the completion of infusion

Phenobarbital
20 mg/kg IV over 10 minutes

Seizures 2 minutes after the completion of infusion

Phenobarbital
10 mg/kg IV over 5 minutes

Seizures 2 minutes after the completion of infusion

Phenobarbital
10 mg/kg IV over 5 minutes

Seizures 2 minutes after the completion of infusion

Fosphenytoin
20 mg PE/kg IV over 10 minutes

Seizures 2 minutes after the completion of infusion

Alternative: Levetiracetam
60 mg/kg IV over 15 minutes

Consider starting maintenance Phenobarbital
5 mg/kg once daily IV/PO
12 hours after the last loading dose

Re-evaluate the need for maintenance treatment prior to discharge

Midazolam infusion
Initial load: 0.15 mg/kg IV
Followed by 2 mcg/kg/min IV infusion
Increase as needed by 2 mcg/kg/min every 10 minutes
Additional 0.15 mg/kg before each increase in infusion rate
Maximum infusion rate: 24 mcg/kg/min

Metabolism/Genetics consult for sequential trial of B6, P5P, folinic acid and biotin
Prognosis

• Underlying etiology is primary predictor of long-term outcomes
  • Febrile seizures in absence of other complications have excellent prognosis

• Failure of compensatory mechanisms in RSE leads to brain damage:
  lesions in cortex and cerebellum and hippocampal sclerosis

• Survivors often have neurological and cognitive deficits

• The risk for developing epilepsy after SE ranges from 22%-40%

• 30 – 40% of SE cases will evolve to refractory status epilepticus
  • Mortality 10 – 40%
  • 15 – 20% → super-refractory status epilepticus
    • Mortality 35 - 65%

• Mortality 10 – 40%

• 15 – 20% → super-refractory status epilepticus
  • Mortality 35 - 65%
Survival by etiology

Survival by age

Summary

• Timely administration of optimal doses of benzodiazepines is of paramount importance in firstline management, with midazolam being preferred agent

• All secondline IV agents (levetiracetam, valproate, phenytoin) are roughly equivalent in terms of efficacy (~50%)

• Reserve IV phenobarbital for use in children <6 mo and SE caused by drug ingestion

• Refractory status epilepticus is very difficult to treat and associated with significantly increased morbidity and mortality

• Standardized treatment protocols and trained staff drive outcomes
Questions

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References