Super-Refractory Status Epilepticus 2014
Pediatric Chula Experience

Definition SE
- Traditional: Prolonged seizure lasting ≥ 30 mins or series of seizure without full recovery to baseline lasting ≥ 30 mins
- Operational: Continuous seizures lasting at least 5 mins or two or more discrete seizures between which there is an incomplete recovery of consciousness
- NCSE: cognitive or behavior change (ranging from mild confusion to coma) coupled with EEG evidence of seizure

Epidemiology CSE
- Incidence of CSE: 10-38/100000 per year
- Bimodal distribution
  - highest in children (age 0-4 years)
  - elderly
- Most common occurred in children less than 1 year
- Associated with poor socioeconomic

Classification of SE
- Generalized convulsive SE
  - Tonic
  - Tonic-clonic
  - Myoclonic
- Generalized nonconvulsive SE
  - Complex partial status
  - Absence status
- Focal SE
  - Epilepsia partialis continua (EPC)

Recommendation of Diagnostic evaluation of a child presenting in SE

<table>
<thead>
<tr>
<th>New onset SE</th>
<th>Known Epilepsy Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always recommended</td>
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</tr>
<tr>
<td>Electrolyte</td>
<td>Electrolyte</td>
</tr>
<tr>
<td>EEG</td>
<td>EEG</td>
</tr>
<tr>
<td>CT/MRI</td>
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</tr>
<tr>
<td>Clinical suspicion</td>
<td>Consider</td>
</tr>
<tr>
<td>Electrolyte</td>
<td>Electrolyte</td>
</tr>
<tr>
<td>Genetic/ Metabolic testing</td>
<td>EEG</td>
</tr>
<tr>
<td>LP</td>
<td>CT/MRI</td>
</tr>
<tr>
<td>Add if febrile</td>
<td>Consider if febrile</td>
</tr>
<tr>
<td>CBC / Hemoculture</td>
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</tr>
<tr>
<td>LP</td>
<td>LP</td>
</tr>
<tr>
<td>Refractory/Persistent encephalopathy</td>
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</tr>
<tr>
<td>- Video EEG monitoring</td>
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</tr>
</tbody>
</table>
New onset SE: Imaging??

- CT/MRI
  - Imaging abnormality 13% to 32%
  - MRI greater sensitivity for cerebral dysgenesis and other cerebral malformation
  - CT scanning may be used in an emergency setting.

New onset SE: EEG??

- EEG
  - Characterize status: Focality
    - Epileptiform discharge
  - Generalise slow
  - Identify: NCSE
  - NCSE
    - After CSE were found to be in NCSE 22%
    - Subclinical seizure 4%

Treatment

- Termination of seizure
- Prevention of seizure recurrence
- Management of precipitating causes
- Management of complication

Treatment: Stabilize patient

- ABCDE
  - Maintain Airway
  - Breathing: Oxygen / Intubation
  - Circulation: IV access
  - Dextrose
  - Electrolyte: Na, Ca, Mg, PO4 and AED level

Stage of treatment SE

 Mayo Clinic
Boston Children’s hospital

5 minutes: Lorazepam, 0.1 mg/kg (usual maximum dose 4 mg/dose); if no IV access, diazepam, 0.5 mg/kg/dose (maximum 20 mg/dose) per rectum
10-15 minutes: Lorazepam, 0.1 mg/kg/dose and start fosphenytoin, 20 mg PE/kg/dose
If fosphenytoin is not available, use phenytoin 20 mg/kg
15-20 minutes: If seizures persist, phenobarbital 20 mg/kg dose
20-30 minutes: If seizures persist, fosphenytoin, 10 mg PE/kg
Consider pyridoxine (Vitamin B6) for infants and children, especially with underlying epilepsy.

Children Hosp. Of Philadelphia (CHOP)

Treatment

- 0-5 min: Oxygen, Airway, Position, Vital sign, IV line
  : Investigation
  : IV glucose / Thiamine /Pyridoxine 100 mg
- 6-30 min: Diazepam 0.3-0.5 mg/kg/dose
  : Phenytoin 20 mg/kg/dose
  : Sodium Valproate 20 mg/kg/dose
  : Levetiracetam 20 mg/kg/dose
- 30+ min: Add PHT/ PB / VPA
- 60+ min: Midazolam 200 mcg/kg/dose bolus
  (Epilepsy Society of Thailand 2011)

Termination of seizure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose &amp; Route</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>0.3 mg/kg IV in 2-5 min</td>
<td>0.5 mg/kg Rectal Max 10 mg</td>
<td>1-3 min Highly lipid soluble</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg IM / IV 0.5 mg/kg Buccal / IN Max 10 mg</td>
<td>Fast acting water soluble</td>
<td>5-30 min</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg IV Max 4 mg</td>
<td>6-10 min</td>
<td>12-24 hr</td>
</tr>
</tbody>
</table>

Prevention of recurrence seizure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage &amp; Route</th>
<th>Rate of infusion</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>20 mg/kg IV</td>
<td>1 mg/kg/min</td>
<td>Phlebitis (pH 11-12) Hypotension</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20 mg/kg IV</td>
<td>3 mg/kg/min</td>
<td>Phlebitis (pH 11-12) Hypotension</td>
</tr>
<tr>
<td>Valproate</td>
<td>20 mg/kg IV</td>
<td>5-6 mg/kg/min</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Levitiracetam</td>
<td>20 mg/kg IV</td>
<td>Rapid infusion</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>20 mg/kg IV / IM</td>
<td>3 mg/kg/min</td>
<td>Prodrug of PHT</td>
</tr>
</tbody>
</table>

Transmucosal pharmacological therapy

- Intranasal midazolam as effective as intravenous diazepam
- Buccal midazolam as effective as rectal diazepam.
- Intravenous formulations of midazolam (given buccal or intranasal routes) are relatively inexpensive.
- Caregivers prefer intranasal midazolam to rectal diazepam.

Appleton R et al Cochrane Database Syst Rev 2008 Jul 16;(3)
Treatment SE

No prospective randomised trials comparing the effects of anaesthetics in the treatment of RSE.

Safety data lacking.

Options:
- Barbiturate anaesthetics: Pentobarbital (US)
  - Thiopental (Europe Aus)
- Propofol
- Midazolam.

Evidence based medicine: No recommendations on data available.

Even in a large survey of neurologists in USA — little consensus for 3rd / 4th line intervention (J Neurol Sci 2003; Rosenow et al; Epileptic Disord 2002; Lall Koul et al; ARCH 1997; Ozdemir et al; Seizure 2005).

Midazolam infusion

- Requires a syringe driver
- Greater risk of airway suppression (especially following previous Benzo boluses)
- Takes long time to gain control (range 15 mins – 4.5 hours)
- Potential for children left with prolonged seizures and irreversible neuronal cell death in centres without high care facilities
- NOTE: Excluded from APLS guidelines

Midazolam

- Standard dosage Midazolam
  - Loading dose 0.2 mg/kg (200 mcg/kg/dose)
  - Maintained at 0.1 to 0.6 mg/kg/hr.
  - (2 mcg/kg/min titrate every 15 min to 10 mcg/kg/min)
- Half-life of 6 to 40 h after prolonged infusion.
- Main drug interactions: None.
- Main side effects: Sedation
  - Respiratory depression
  - Hypotension > Inotropic drug

Thiopentone

- Poor anticonvulsant
- Marked haemodynamic effects
- Prolonged drug effects if infusion used
- Local ICU capacity limited
- Staffing
- Monitoring
- Anaesthetic experience
Very-high-dose Phenobarbitone

- Both barbiturates and benzodiazepines exert a primary effect on the GABA receptor complex.
- No antiepileptic ceiling effect! No maximum dose beyond which further doses are likely to be ineffective >200 mg/kg!

Complications:
- Sedative and respiratory-depressant properties more likely in combination with benzodiazepines.
- Hypotension unusual and related to the highest Phenobarbitone levels and easily controllable.
- Complications usually related to underlying aetiology

Crawford et al; Neurol 1988

Intravenous Sodium Valproate

- FDA approved 1996.
- Not in APLS guidelines
- No reports of respiratory depression or hypotension.
- Caution in children with underlying liver disease or suspected mitochondrial disorder.
  - Potential hepatic encephalopathy
- Comparative studies:
  - Intravenous Sodium Valproate vs Diazepam infusion
  - Intravenous Sodium Valproate vs Phenytoin.
- No large studies measuring efficacy
- Larger paediatric focused studies are needed
  - Still need syringe driver
  - Very expensive
  - Drug of choice: Absence status

IV Levetiracetam

- FDA approved adults over 16 yrs since 2006
- Limited data in children (most retrospective case reviews – n=10 and n=32)
- Loaded with 25-50mg/kg at level 3
- Effective
- Safe
- Larger comparison studies needed

Kirmani et al Ped Neurol 2009
Ahmed et al Pediatr Emerg Care Med 2009
Gonza-Layen et al CND Drugs 2009

Why is IV phenobarbitone so good for resource poor countries?

- Highly effective at controlling status
- Safe
- Cheap
- It can be given by rapid IV bolus
- It can be repeated
- It can be given by IM route
- No need for syringe driver
- If control not attained at 1 hour time to arrange transfer to tertiary unit – exceptional situation

Crawford et al; Neurol 1988;
Wilmhurst & Newton; DMCN 2005
Lee et al;Pediatr Neurol 2005

Lacosamide

- Adult :Bolus dose 400 mg (range 200–400 mg), Rate 40–80 mg/min
  - Success Rate: 1st AED: 3/5, 2nd AED: 11/19, > 4th AED: 3/15 Failed in 5 subjects, No seizure adverse events
  - 2009-2010 review: 532 SE (486 adults / 46 children), overall LCM efficacy 57% comparable in nonconvulsive and generalised-convulsive (57%/61%);
  - Better in focal motor SE (92%: p = 0.015; p < 0.001);
  - If LCM used as later AED: Eff drop from 100% ->20%.
  - AE: dizziness, abnormal vision, diplopia, and ataxia.
- Pediatric: Bolus 8.7 mg/kg (up to 10 mg/kg), Total first 24 hour 13.8 mg/kg
  - Success 77.8%/7/9, Sev free 44.4 (4/9), failed 2/9
  - 50% to 50% of children experienced at least a 50% reduction in seizure frequency, similar to results obtained in clinical trials in adults. Children with focal onset seizures were most likely to benefit from treatment

Kellinghaus et al; Acta Neurol Scand 2010;
Strichra et al; Epilepsia 2011;
Poddar et al; J.pediatrneurol.2016

Outcome and Prognosis SE

- Factor determine risk of mortality and morbidity
- Certain etiology
- Age
- Long duration of SE
- Mortality rates
  - Short term during the first 30-60 days after SE mortality rate 7-25%
  - unprovoked or febrile CSE 0.2%
  - acute symptomatic CSE 12.5-16%
Neurologic sequelae

- Secondary epilepsy
- Cognitive deterioration
- Behavioral problems
- Focal neurologic deficit

Refactory SE ??

- Review diagnosis: True seizure ??
  - Abnormal movement
  - Psychogenic nonepileptic seizures
- Review Treatment: Adequate ??
**Differential diagnosis of CSE**

- Tonic extensor spasm
  - tentorial herniation
  - acute brainstem dysfunction
- Acute dystonic reaction
- Chorea
- Paroxysmal dyskinesia
- Psychogenic status epilepticus

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**Clinical features of epileptic seizures versus psychogenic nonepileptic seizures**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Epileptic seizures</th>
<th>Psychogenic nonepileptic seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye closed</td>
<td>Uncommon</td>
<td>Very common</td>
</tr>
<tr>
<td>Stereotypic Sz semiology</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>Sz duration &gt; 2 mins</td>
<td>Uncommon</td>
<td>common</td>
</tr>
<tr>
<td>Sz onset at sleep</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Enuresis</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Injury</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Medial tongue bite</td>
<td>Common</td>
<td>Uncommon (Tip of tongue)</td>
</tr>
</tbody>
</table>

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**Refractory SE**

- Consult: neurologist
- EEG Monitoring
- Look for treatable cause: autoimmune encephalitis
- Refer

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**Brain Monitoring**

- Continuous
- Non-invasive
- Highly sensitive to a variety of brain insults
- Reasonably specific
- User friendly
- Not too expensive!

_Kurtz et al. Curr Opin Crit Care 2009_

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**Monitoring**

- cEEG (continuous EEG – full head montage)
  - The Gold standard – not viable in most SA settings
  - Non-convulsive seizures
  - Ischaemia
- aEEG (Amplitude-integrated EEG)
  - Assessing if burst suppression attained
  - Non-convulsive seizures
  - Potential artefact
- Need to remember overall underlying cause usually the defining feature for the outcome of the child.
Non Pharmacological Rx: SRSE

- Ketogenic Diet
- IV Methyl Prednisolone (In specific cases)
- IVIG
- Surgical Resection
- VNS
- (Case to be presented during the meeting)