Management of Status Epilepticus & Super-Refractory SE 2017

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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 years
- 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>
</table>
| Always recommended  
  - Electrolyte  
  - EEG  
  - CT/MRI | Always recommended  
  - AED level |
| Clinical suspicion  
  - Urine toxicology  
  - Genetic/ Metabolic testing  
  - LP | Consider  
  - Electrolyte  
  - EEG  
  - CT/MRI |
| Add if febrile  
  - CBC / Hemoculture  
  - LP | Consider if febrile  
  - CBC / Hemoculture  
  - LP |
| Refractory/Persistent encephalopathy  
  - Video EEG monitoring | Refractory/Persistent encephalopathy  
  - Video EEG monitoring |
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
    - 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

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

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

- Stage 3: Refractory Status Epilepticus
  - Treat with general anesthesia: for instance, propofol, midazolam, or thiopental/propofol

Super-refractory Status Epilepticus: Status epilepticus which has continued or recurrent despite therapy with general anesthesia for 24 hours or more
Boston Children’s hospital

- 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
  Phenobarbital 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

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>1-5 min</td>
<td>Highly lipid soluble</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg IM/IV</td>
<td>Fast acting water soluble</td>
<td>3-5 min</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg IV</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)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>20 mg/kg IV</td>
<td>3 mg/kg/min</td>
<td>Sedation, Arrhythmia</td>
</tr>
<tr>
<td>Valproate</td>
<td>20 mg/kg IV</td>
<td>3.6 mg/kg/min</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Levetiracetam</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>

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.

Treatment of refractory SE

- No prospective randomised trials comparing the effects of anesthetics in the treatment of RSE.
  - Safety data lacking.

  Options:
  - Barbiturate anesthetics: 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)

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

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

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 etiology
  
  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

Complications:
- Intravenous Sodium Valproate vs Diazepam infusion
- Intravenous Sodium Valproate vs Phenytoin.
- No large studies measuring efficacy
- Larger randomized, controlled 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


**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; Wilmshurst & Newton; DMCN 2005; Lee et al, Pediatric Neurol 2005

**Lacosamide**

- Adult: Bolus dose 400 mg (range 200–400 mg), Rate 40–80 mg/min
  - Success Rate 47–57%
  - AED: 1/3, 2nd AED: 3/17, 3rd AED: 11/19, 4th AED: 3/15 Failed in 5 subjects, No serious adverse events
  - 2006–2008 review: 592 SE cases (461 adults/36 children), overall LCM efficacy 57%; comparable in nonconvulsive and generalized-seizures (57%/61%
  - Better in focal motor SE (92%; p < 0.03); p < 0.001)
  - If LCM used as later AED: Efficacy drop from 50% to 30%
  - All: 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%/48%
  - For free 4:4 (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


**What to do when Midazolam drip failed?**

**Duration of therapy:** Pharmacologic coma duration should be determined and limited to 24-48 hours, with early determination made by considering seizure response, overall EEG and clinical improvement, and time required to initiate or modify other anti-seizure medications. The mean time should be determined and is often 24-48 hours, with early determination made by considering EEG and clinical improvement.

**Criteria for transitioning to or adding additional anti-seizure agents:** If seizures persist after 4 hours, on high-infusion doses, or adverse effects. Note: transitioning to additional medications may be appropriate. If seizures are somewhat improved or tolerate the agent effectively, then addition of an additional medication may be appropriate.

- Patients < 10 kg: Choose Midazolam 3 mg/ml, concentration at the initiation of the infusion protocol. After infusing over 4 hours, change the concentration to 5 mg/ml.
- For patients on the ketogenic diet, ensure that the patient is normal stable.
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%

F 10 Year Old Mida 12 mic / Propofol 4/Acidosis

- Midazolam bolus 0.2 mg/kg -> No changes
- Already on Ketogenic diet, urine ketone 2+
- Tx from Saraburi on Pheno/VPA bl level 150/9 mg/kg/min
- On Propofol to max 10 mic/kg/min-> developed acidosis / CPK 500 / drop propofol -> Sz recurred
- Phenobarbital level 102 mg/dl
- What Would you like to do ?
- Bolus 5 mg/ 1st dose : no changes
- Bolus 5 mg/ 2nd dose : Burst Suppress ☺

Just before next dose : Observation
- It's OK : Continue Observation
Add 2mg/kg IV Phenobarbital Bolus

Neurologic sequelae

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

REVIEW ARTICLE
The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy

Simon Stovin and Monica Tofar
Refractory 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

Clinical features of epileptic seizures versus psychogenic nonepileptic seizures

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<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>Stereotyped 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>Faintness</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>
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</table>

Refractory SE

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

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.

Case Report:
A case of frontal lobe epilepsy in which amplitude-integrated EEG combined with conventional EEG was useful for evaluating clusters of seizures

Ketogenic Diet : PT

- A 10 year old Thai female
  - Intractable left frontal lobe seizure since age of 4 year old
  - Functions : Can do all activity of daily living by herself but slow & never go to school : IQ 68
  - Developed Status Epilpticus \rightarrow Intubated \rightarrow PHT/Phenobarbital/NPA/Midazolam IV
  - Transferred to the ward with IV Midazolam

Non Pharmacological Rx : SRSE

- Ketogenic Diet
- IV Methyl Prednisolone (In specific cases)
- IVIG
- Surgical Resection
- VNS
- (Case to be presented during the meeting)
Ketogenic Diet Started -> seizure subsided in one week, urine ketone 2-3 +
The patient was seizure free x 3 months then developed rare nocturnal seizures
She refused to take ketogenic diet after one year! -> readmitted with status epilepticus
Left frontal lobe resection -> Partial improvement
Zonegran was started with ketogenic diet
Require constant dose adjustment

Functional Hemispherectomy
PK: A nine year old Thai boy who was previously healthy
Two years ago he developed right hand and finger abnormal movement which gradually stopped spontaneously
Developed seizure with no fever in Dec 2013, received PHT -> well controlled x 1 1/2 months.
Developed fever with rash -> PHT was stopped
Rt side clonic seizures recurred and gradually become continuous in two weeks. -> Intubated -> Rx in ICU

DDx Mitochondria
Transferred to Chula via 12 hours ambulance from Songkhla

EEG Monitoring Focal SE (EPC)
CFM -> Titration of Keppra, Phenobarb up and add lacosamide
Seizure improved, regain consciousness but Rt side EPC persisted.
EEG Monitoring Focal SE

MRI Jan 2014 vs Feb 2014

S/P Left Functional Hemispherectomy

- Repeat MRI Obtained -> Progressive increased in T2 changes
- Dx : Rasmussen encephalitis
- Mtx functional hemispherectomy
A 3 year old with status epilepticus