Pediatric Neurological Emergencies – I

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- I have no financial disclosure
Upon completion of this activities participant will be able to:

- Distinguish different types of febrile seizures
  Differentiate febrile seizures and non febrile seizures and their managements

- Distinguish status epilepticus
  Discuss status epilepticus management

Outlines

- Approach to a child with fever and seizure

- Childhood febrile seizures
  - Classifications, Clinical features, Managements

- Seizure and Epilepsy
  - Definitions, Classifications

- Status Epilepticus, Refractory Status Epilepticus, Super Refractory Status Epilepticus
  - Definition, Diagnosis and Classifications, Etiologies, Epidemiology Managements
Approach to child with fever and seizure

• Well looking child vs sick child
• Good description of the event
  • Before
  • First event
  • Other symptoms
    • Altered mental status, irritability, focal neurological signs, ataxia, difficulty with speech
• Family history

Approach to a child with fever and seizures

Childhood febrile seizures is a diagnosis that can be made ONLY after infectious causes of seizures with fever are ruled out
When to consider a Lumbar Puncture

- AAP: Strongly consider in infants under 12 months of age with a first complex febrile seizure as well as any child with lethargy
  - Seizure in the ED
  - Focal or prolonged seizure
  - Seen a physician within the past 48 hours
  - Concern about follow-up
  - Prior treatment with antibiotics

CNS infections

- <1 months old
  - GBS, E. Coli, Listeria
  - Amp + Cefotaxime/ (Gent neonate)
- 1-3 month
  - GBS, S. pneumo, H flu, N meningitis, E.coli
  - Amp + cefotaxime/ceftriaxone
- >3 month
  - S.pneumo, N.meningitis, H.flu,
  - Ceftriaxone/ Vancomycin
- Herpes meningoencephalitis (Acyclovir)
Childhood febrile Seizures

- < 10-15 mins
- No focal features
- No greater than 1 episode in 24h
- Neurologically and developmentally normal

Childhood febrile seizures

- Age 6 months to 5 years
- Fever (and seizure) not caused by meningitis, encephalitis, or any other illness affecting the brain

Simple febrile seizure
- < 10-15 mins
- No focal features
- No greater than 1 episode in 24h
- Neurologically and developmentally normal

Complex febrile seizure
- >10-15 min
- Focal
- Recurrence within 24h
Management

- Although scary, most of the time it is not an emergency
- No need for antiepileptic medications
- The use of antipyretics does not reduce the risk for febrile seizures.
- Prescribe rescue medication, an appropriate dose!
- Patient should be followed up by the PCP

Risk of recurrent febrile seizures: 30%
Decline in IQ
Increased risk of epilepsy
Death 30%
Definitions

- Seizure: the clinical manifestation of an abnormal and excessive synchronization of a population of cortical neurons

- Epilepsy: tendency toward / risk for recurrent seizures unprovoked by any systemic or acute neurologic insult

Type of seizures

- Focal: Seizures arising from a focal area of the brain.
  - Focal without alteration of awareness (Simple partial) (focal seizure wo impaired awareness)
  - Focal with alteration of awareness (Complex partial) (focal seizure with impaired awareness)
Generalized: Seizures which involve the entire brain.

Types:
- absence
- myoclonic
- clonic
- Tonic
- tonic-clonic
- atonic seizures.

History of Physical examination
- Get a good description of the spell
- Duration of the spell
- Partial vs generalized onset
- Auras
- Alteration of consciousness
- Other symptoms
- Family history
- Birth history and developmental milestones
- Epilepsy risk factors
- Through physical examination with neuro exam
Take home message

- Do not routinely need imaging if neurological physical exam is normal.
- Avoid CT scan because of exposure to radiation
- Prescribe rescue medication
- Childhood febrile seizures is a diagnosis that can be made ONLY after infectious causes of seizures with fever are ruled out

Status Epilepticus
Evolution of the definition

- 30 minutes EFA Working Group on SE, 1983
- 20 minutes Bleck, 1991
- 10 minutes Treiman et al., 1998
- 10 minutes Lowenstein et al., 1999
- 5 minutes Alldredge et al., 2001

Epilepsy Foundation of America Working Group on SE, JAMA. 1983; 270: 854-9
Bleck TP, Clin Neuropharmacol. 1993; 14: 191-8
Lowenstein DH et al., Epilepsia. 1999;40: 120-2
### Diagnosis and Classification of Status Epilepticus

- >5 min of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures
- **Classification**
  - **Convulsive SE**
    - Convulsions associated with rhythmic jerking of the extremities
  - **Non-convulsive SE**
    - EEG seizure activity without the clinical findings associated with convulsive SE
  - **Refractory SE**
    - SE that does not respond to the standard treatment
      - Initial benzodiazepine followed by another AED
  - **Super Refractory SE**
    - Continuous seizures despite 24 hr of adequate burst-suppression with an anesthetic agent (3rd-line therapy) or recurrence after stopping the anesthetic agent

### Epidemiology

- 2nd most frequent neurological emergency
- Incidence in the general population: 20-40/100,000 per year in the US
- 2 peaks, before age 1 and after age 60
- SE maybe refractory to 1st and 2nd line AED in 30-40% of cases
- ~20% of patients with SE die within the first 30 days
- 55,000 deaths / year
Cont.

- 25% of SE occurs in epilepsy patients
- 15% of epilepsy patients experience SE
- 10% of epilepsy patients present with SE
- 25% non-convulsive SE (NCSE)
- In the hospital settings NCSE affects: up to 10% of patients with altered level of consciousness
- 16% of “confused” elderly

Etiology

- In children <2 yo → >80% infection or acute febrile illness
  - In 2-16 yo → Infection is 36%
  - In adults only 5% is due to infection
  - Stroke causes 27% of status epilepticus in adults and <2% in children
Etiologies

**Causes in Adult**
- Idiopathic 30%
- Acute symptomatic 50%
- Febrile 0%
- Remote symptomatic 10%
- Encephalopathy 10%

**Causes in Children**
- Idiopathic 30%
- Acute symptomatic 35%
- Febrile 25%
- Remote symptomatic 15%
- Encephalopathy 5%

Principle of Management

- Prompt treatment to prevent morbidity and mortality
- Tailor aggressiveness of treatment for RSE to the clinical situation
- Focal RSE w/o impairment of consciousness might initially be approached conservatively
- In generalized convulsive SE, early induction of pharmacological coma is advisable
- Treatment lasting weeks or months can sometimes result in a good outcome

Emergent Initial therapy

• Evidence supports and experts agree that benzodiazepines should be the agent of choice for emergent initial treatment.

• Intravenous (IV) administration is preferred.
  ➢ Benzodiazepines can be administered via intramuscular (IM), rectal, nasal, or buccal routes when IV therapy is not feasible.
  ➢ For IV therapy, lorazepam is the preferred agent.
  ➢ Midazolam is preferred for IM therapy (and can also be given nasally or buccally).
  ➢ Diazepam is preferred for rectal administration.

Cont.

• Controlled studies have evaluated lorazepam versus diazepam, phenobarbital, phenytoin, and IM midazolam.¹ ² ³

  IM midazolam was found to be at least as effective as IV lorazepam in pre-hospitalized patients with SE.

  In a randomized, controlled trial, respiratory depression was seen less frequently in those treated with benzodiazepines for GCSE than for those who received placebo.¹

  ³ Leppik IE, JAMA. 1983;249(11):1452–4. 84
Urgent treatment

- Urgent control AED treatment following administration of short acting benzodiazepines is required in all patients who present with SE

- There are two potential goals of urgent control therapy...
  - For patients who respond to emergent initial therapy......
  - For patients who fail emergent therapy......

- There is conflicting data and differences in expert opinion about which agent is most effective for urgent control and the choice often varies based on the particular patient scenario.
The preferred top tier agents that are generally used for urgent control of SE are:

- IV Fosphenytoin/Phenytoin, Valproate sodium, Phenobarbital, Levetiracetam, or continuous Midazolam infusion.

Of these agents

- Fosphenytoin preferred for most patients with the exception of patients (particularly children) with a history of primary generalized epilepsy, where valproate sodium would be the best choice.

One study suggested that IV valproate sodium may have similar efficacy as urgent control therapy when compared to phenytoin. 1,2,3

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Table 6: Treatment recommendations for SE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Class/level of evidence</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Class I, level A</td>
<td>[19, 30, 42, 93, 98]</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Class I, level A</td>
<td>[94, 99-100]</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Class I, level A</td>
<td>[10, 23, 95, 97-100, 107, 109-114]</td>
</tr>
<tr>
<td>Phenytoin/Fosphenytoin</td>
<td>Class II, level A</td>
<td>[111, 92, 96, 115-119]</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Class II, level A</td>
<td>[10, 97, 114]</td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Class II, level A</td>
<td>[116, 117, 119-122]</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class II, level C</td>
<td>[115, 122-128]</td>
</tr>
<tr>
<td><strong>Urgent treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Class II, level A</td>
<td>[117, 120-122, 131-134]</td>
</tr>
<tr>
<td>Phenytoin/Fosphenytoin</td>
<td>Class II, level B</td>
<td>[15, 23, 95, 97-100, 115, 119, 131, 133, 135]</td>
</tr>
<tr>
<td>Midazolam (continuous infusion)</td>
<td>Class II, level C</td>
<td>[116, 131]</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Class II, level C</td>
<td>[139, 141]</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class II, level C</td>
<td>[115, 122-128, 130, 140, 141]</td>
</tr>
<tr>
<td><strong>Resistant treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Class II, level B</td>
<td>[118, 106-108, 143-150]</td>
</tr>
<tr>
<td>Propofol</td>
<td>Class II, level B</td>
<td>[135, 150]</td>
</tr>
<tr>
<td>Phenobarbital/thiopental</td>
<td>Class II, level B</td>
<td>[136, 154]</td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Class II, level B</td>
<td>[137, 120, 133, 135, 156-158]</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class II, level C</td>
<td>[137, 150]</td>
</tr>
<tr>
<td>Phenytoin/Fosphenytoin</td>
<td>Class II, level C</td>
<td>[135, 150]</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Class II, level C</td>
<td>[136-138]</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Class II, level C</td>
<td>[149]</td>
</tr>
<tr>
<td>Phenytoin/Phenobarbital</td>
<td>Class II, level C</td>
<td>[135]</td>
</tr>
</tbody>
</table>

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In most cases of SE, continuous EEG and/or clinical exam will determine the persistence of SE after both emergent initial and urgent control AED treatments have been given.

If refractory SE, recommended; to immediately start additional agents.

The main decision point at this step is to consider; repeat bolus of the urgent control AED or to immediately initiate additional agents.

If attempts to control the SE with bolus intermittent therapy fails, treatment recommendations → continuous infusion AEDs to suppress seizures.

If the first continuous infusion or AED chosen for RSE fails → switching to a different continuous infusion or starting another agent.

The use of Valproate sodium, Levetiracetam, and Phenytoin/Fosphenytoin in intermittent boluses may also be considered if they have not previously been administered.
At present, there are insufficient data to suggest whether Midazolam, Propofol, or Pentobarbital is the preferred agent. 1,2

- Propofol is an option but its safety profile needs to be considered as it can cause Propofol infusion syndrome.

- Midazolam may cause less hypotension as it does not contain the solvent propylene glycol and may be preferred in selected clinical situations.

- Pentobarbital may have a higher rate of successfully controlling RSE acutely than midazolam, but may have more adverse effects.

Table 8 RSE dose recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dose</th>
<th>Continuous infusion dose recommendations (infusion rate to DEG)</th>
<th>Severe adverse effects</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Midazolam    | 0.2 mg/kg, admixture of an infusion rate of 1 mg/min | 0.05-0.2 mg/kg CI infusion rate of 1 mg/min, increase CI rate by 0.05 mg/kg every 3 h | Respiratory depression | Hypersalivation, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause respiratory depression, may cause 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- Pentobarbital may have a higher rate of successfully controlling RSE acutely than midazolam, but may have more adverse effects.
Cont

• Pediatric SE
  There is no evidence that children respond differently to AED treatment than adults.
  
  ➢ Pharmacokinetic differences, risk of adverse events (e.g., Popofol infusion syndrome) and syndrome specific treatment should be considered to optimize therapy for SE.
  
  ➢ Concern exists for possible hepatotoxicity when using valproate sodium in younger children (<2 years of age), especially those with a metabolic or mitochondrial disorder.

SE treatment

• Stabilization phase
• 1st line
  • Benzodiazepine
    ➢ IV: Lorazepam, Diazepam, Midazolam
    ➢ IM: Midazolam, Diazepam
    ➢ Rectal: Diazepam
    ➢ Intranasal, Buccal: Midazolam
Cont.

- 2\textsuperscript{nd} line agents
  - Phenytoin /Fosphenytoin/ LEV/ VPA
- 3\textsuperscript{rd} line agents
  - Phenobarbital /......

➢ Patient should be in the PICU and you should consider intubation

Cont.

SE treatment considerations

- Brief directed Hx
- CMP, CBC, Cultures, drug level, tox screen
- Correct electrolytes
- Antibiotics/Antivirals
  ➢ If meningitis/encephalitis considered
Refractory SE

- Midazolam drip (Versed)
- Propofol
- Inhalational anesthesia,
- Induce barbiturate coma- pentobarbital

The aim of treatment is to put the patient in coma
**Time is brain!**

- Mortality in pediatric status epilepticus 4%
- Morbidity may be as high as 30%
  - Animal studies: permanent changes after 30 minutes, and neuron loss at 1 hour
  - Human studies: increased morbidity and mortality correlating with the duration of SE

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**Emergent EEG**

- Not generally available on emergent basis
  But consider in...
  - Persistent altered mental status (? Electrographic/non-convulsive status epilepticus)
  - Paralyzed patients
  - Pharmacologic coma
Recommendations

- Make the diagnosis promptly, including the type of SE.
- Treat soon, and adequately, BNZ first line!!!
- Choose treatment for the appropriate type of SE.
- Do not forget the underlying cause.
- Use the guidelines and clinical judgment!
- MDZ, PRO, PNT judiciously, often MDZ, PRO first, later PNT.
- Intensive medical care!

Thank you