Seizure Management in the Acute Care Setting

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Learning Objectives

• Identify the physiology of seizures in the pediatric patient.

• Recognize various types of seizure presentations in pediatric patients.

• Utilize physiologic understanding in preparing a differential diagnosis of the etiology of seizures in the acute care setting.

• Prepare diagnostic and treatment plans, with appropriate modification based on clinical course.
Defining a Seizure Begins with Understanding Function at the Cellular Level

The brain functions and communicates through electricity:

1. Neurons Create an Impulse
2. Neurotransmitter Released
3. Travels Along Axons
4. Impulse Either Excites or Inhibits

(Freeman et. al., 1990)
A seizure is the result of imbalance between inhibitory and excitatory impulses.

The balancing point between excitation and inhibition is the seizure threshold.

Factors that lower seizure threshold:
- Younger age
- High fever
- Genetics
- Chemical variations
- Excitement
- Lack of sleep
- Focal region of injury

Factors that raise seizure threshold:
- Older Age
- Anticonvulsant Drugs
- Balanced Lifestyle

(Freeman et. al., 1990)
How we Define Seizures

The physical and electrographic characteristics guide our localization and definitions of seizures:

Focal or Multifocal Seizures

- Simple Partial
- Complex Partial
  - Impairment of consciousness at onset or
  - Partial onset with progressive impairment of consciousness
- Partial with Evolution to Generalized

Generalized Seizures

- Epilepsy
- Febrile Seizures
- Neonatal Seizures

(Agarwal and Fox, 2013)
(Swaiman and Ashwal, 1999)
Further Defining Seizure Presentation

(Fisher et al., 2017)
Electrographic Elements of Generalized Seizure

Left Side Leads, Odd Numbers

Vertex Leads

Right Side Leads, Even Numbers
Electrographic Elements of Generalized Seizure
Clinical Elements of Generalized Seizure
Seizure presentation and focality guides the development of a differential diagnosis in the acute care setting.

- Patient with a history of seizures
- Patient without a history of seizures

In either group, why are they presenting with seizures?

(Abend et. al., 2013)
In the Patient Without a History of Seizures

V: vascular

I: infection

T: trauma

A: autoimmune

M: metabolic, ingestion

I: inflammation

N: neoplasm

Table 2 Potential underlying etiology

<table>
<thead>
<tr>
<th>Acute processes [8, 12]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic disturbances: electrolyte abnormalities, hypoglycemia, renal failure</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Central nervous system infection: meningitis, encephalitis, abscess</td>
</tr>
<tr>
<td>Stroke: ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, cerebral sinus thrombosis</td>
</tr>
<tr>
<td>Head trauma with or without epidural or subdural hematoma</td>
</tr>
<tr>
<td>Drug issues</td>
</tr>
<tr>
<td>Drug toxicity</td>
</tr>
<tr>
<td>Withdrawal from opioid, benzodiazepine, barbiturate, or alcohol</td>
</tr>
<tr>
<td>Non-compliance with AEDs</td>
</tr>
<tr>
<td>Hypoxia, cardiac arrest</td>
</tr>
<tr>
<td>Hypertensive encephalopathy, posterior reversible encephalopathy syndrome</td>
</tr>
<tr>
<td>Autoimmune encephalitis (i.e., anti-NMDA receptor antibodies, anti-VGKC complex antibodies), paraneoplastic syndromes</td>
</tr>
</tbody>
</table>

(Brophy et. al., 2012)
In the Patient With a History of Seizures

In a patient with epilepsy we consider the acute processes, we also consider circumstances that can affect seizure threshold:
• Maintenance anti-epileptic regimen, and therapeutic levels
• Evolving bacterial or viral illness
• External stimulation
• Sleep disturbances
• Gastrointestinal complications, and poor absorption

Table 2 Potential underlying etiology

<table>
<thead>
<tr>
<th>Chronic processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting epilepsy: breakthrough seizures or discontinuation of AEDs</td>
</tr>
<tr>
<td>Chronic ethanol abuse in setting of ethanol intoxication or withdrawal</td>
</tr>
<tr>
<td>CNS tumors</td>
</tr>
<tr>
<td>Remote CNS pathology (e.g., stroke, abscess, TBI, cortical dysplasia)</td>
</tr>
<tr>
<td>Special considerations in children</td>
</tr>
<tr>
<td>Acute symptomatic SE is more frequent in younger children with SE [33]</td>
</tr>
<tr>
<td>Prolonged febrile seizures are the most frequent cause of SE in children [34]</td>
</tr>
<tr>
<td>CNS infections, especially bacterial meningitis, inborn errors of metabolism, and ingestion are frequent causes of SE [34, 35]</td>
</tr>
</tbody>
</table>

(Brophy et. al., 2012)
The Next Steps in Building a Differential Diagnosis

Table 3  Suggested diagnostic work-up [21]

The steps included in the diagnostic work-up should be completed as soon as possible and occur simultaneously and in parallel with treatment.

<table>
<thead>
<tr>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fingerstick glucose</td>
</tr>
<tr>
<td>2. Monitor vital signs.</td>
</tr>
<tr>
<td>3. Head computed tomography (CT) scan (appropriate for most cases)</td>
</tr>
<tr>
<td>4. Order laboratory test: blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, AED levels.</td>
</tr>
<tr>
<td>5. Continuous electroencephalograph (EEG) monitoring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consider based on clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Brain magnetic resonance imaging (MRI)</td>
</tr>
<tr>
<td>2. Lumbar puncture (LP)</td>
</tr>
<tr>
<td>3. Comprehensive toxicology panel including toxins that frequently cause seizures (i.e. isoniazid, tricyclic antidepressants, theophylline, cocaine, sympathomimetics, alcohol, organophosphates, and cyclosporine)</td>
</tr>
<tr>
<td>4. Other laboratory tests: liver function tests, serial troponins, type and hold, coagulation studies, arterial blood gas, ABD levels, toxicology screen (urine and blood), and inborn errors of metabolism</td>
</tr>
</tbody>
</table>

*AED* antiepileptic drug

(Brophy et. al., 2012)
Most Importantly, Treatment of the Seizures

- Most pediatric seizures are brief and self-limited.
- But when a seizure persists, we must be quick to recognize, and initiate treatment.
- The longer a seizure persists, the more difficult it becomes to manage with medications.

(Kazl and LaJoie, 2020)

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<table>
<thead>
<tr>
<th>Time Line</th>
<th>Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 min</td>
<td>Stabilizing patient (airway, breathing, circulation, disability - neurologic exam)</td>
</tr>
<tr>
<td>2-5 min</td>
<td>Time seizure from onset, monitor vital signs</td>
</tr>
<tr>
<td>3-4 min</td>
<td>Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed</td>
</tr>
<tr>
<td>4-5 min</td>
<td>Initiate ECG monitoring</td>
</tr>
<tr>
<td>5-10 min</td>
<td>Collect finger stick blood glucose. If glucose &lt; 60 mg/dl then</td>
</tr>
<tr>
<td></td>
<td>Adults: 100 mg bolus IV then 50 mg D5W IV</td>
</tr>
<tr>
<td></td>
<td>Children &lt; 2 years: 2 mg/kg D5W IV</td>
</tr>
<tr>
<td></td>
<td>Children &lt; 2 years: 0.5 mg/kg D13.5W</td>
</tr>
<tr>
<td></td>
<td>Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels</td>
</tr>
</tbody>
</table>

**A benzodiazepine is the initial therapy of choice (Level A):**

- Choose one of the following 2 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 (0.15-0.3 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 (0.2-0.3 mg/kg, max 20 mg/dose, single dose, Level B) OR
- Intranasal midazolam (Level B), buccal midazolam (Level B)

**There is no evidence based preferred second therapy of choice (Level I):**

- Choose one of the following second line options: and give as a single dose
  - Intravenous fosphenytoin (30 mg/kg/dose, max 1500 mg/dose, single dose, Level I) OR
  - Intravenous valproic acid (40 mg/kg, max 3000 mg/dose, single dose, Level I) OR
  - Intravenous levetiracetam (60 mg/kg, max 4500 mg/dose, single dose, Level I)

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)

**There is no clear evidence to guide therapy in this phase (Level I):**

- Choices include: repeat second line therapy or a therapeutic dose of either thiopental, midazolam, pentobarbital, or propofol (all with continuous ECG monitoring)

Fig. 2. Hospital convulsive status epilepticus management algorithm, American Epilepsy Society.
Table 2 Antiepileptic Drugs Approved for the Treatment of Seizures in the U.S.

<table>
<thead>
<tr>
<th>Primary Generalized Tonic–Clonic Seizures</th>
<th>Partial Seizures*</th>
<th>Absence Seizures</th>
<th>Atypical Absence Myoclonic, and Atonic Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Carbamazepine</td>
<td>Valproic acid</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Phenobarbital</td>
<td>Ethosuximide</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Oxcarbazepine</td>
<td></td>
<td>Topiramate</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alternative agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonisamide†</td>
<td>Levetiracetam†</td>
<td>Lamotrigine</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Topiramate†</td>
<td>Clonazepam</td>
<td>Felbamate</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tiagabine†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Zonisamide†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Gabapentin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>Phenobarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>Primidone</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Felbamate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Eslicarbazepine</td>
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<td></td>
<td>Vigabatrin</td>
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<td></td>
<td>Lacosamide</td>
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<td></td>
<td>Pregabalin</td>
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<td></td>
<td>Rufinamide</td>
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</tr>
</tbody>
</table>

* Includes simple partial, complex partial, and secondarily generalized seizures.
† As adjunctive therapy.


(Goldenberg, 2010)
Treatment Approaches to Pediatric Seizures

First Line Management: Benzodiazepine

- Selection of agent may be institution and accessibility dependent
- Pediatric convulsive seizures resolved with first-line therapy in 42% of patients

Second Line Management:

- Selection of agent may depend on patient's seizure history, and suspected etiology of seizures
- Data proving comparable efficacy of Fosphenytoin, Levetiracetam, and Valproic Acid
- Pediatric convulsive seizures resolved with second-line therapy in 35% of patients

Third Line Management:

- Should be initiated within sixty-minutes of seizure onset in patient's refractory to first- and second-line therapy

(Abbend and Loddenkemper, 2014)
(agarwal and Fox, 2013)
(Kazl and LaJoie, 2020)
A Case Study of Focal Seizures
The Electrographic Correlate of a Focal Seizure
The Clinical Correlate of a Focal Seizure
“Status epilepticus is a condition resulting either from failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures… It is a condition that can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.”

(Kazl and LaJoie, 2020)
Understanding Status Epilepticus

Status Epilepticus: either continuous tonic-clonic seizure activity lasting greater than five minutes, or recurrence of seizures without return to baseline in a five-minute period.

• The most common neurologic emergency worldwide, with a proposed prevalence of 15 – 40 cases per 100,000 people.
  • One study estimates pediatric long-term mortality up to 22%
• The definition of status epilepticus has evolved from previous parameters defined by 30 minutes of seizure activity.
• We now realize how difficult it is to stop a generalized seizure that persists beyond five minutes, and the neurologic injury related to continued seizure activity.

(Kazl and LaJoie, 2020)
Status epilepticus can result in multi-system involvement:

**Cerebral**
- Hypoxic/Metabolic Derangements
- Excitotoxic Damage
- Edema and Increased ICP
- Venous Thrombosis, Infarct, Hemorrhage

**Cardiac**
- Hypo/Hypertension
- Cardiac Failure
- Arrhythmia/Arrest

**Respiratory**
- Apnea, Abnormal Respiratory Pattern
- Pulmonary Edema, Pneumonia, Aspiration, Embolus

**Autonomic**
- Sweating, Hyperthermia

**Metabolic**
- Hypoglycemia, Electrolyte Derangements
- Acidosis
- Acute Renal or Hepatic Failure
- DIC
- Rhabdomyolysis
- Infections
- Fractures

(Fisher et al., 2017)

(Chin et al., 2006)
Know how to find your seizure pathway, it will walk you through treatment paths.
And, When the Seizures Continue

Refractory Status Epilepticus: continuous seizure activity that is not controlled by first- and second-line medications.

- Estimated prevalence of 9% to 43% between pediatric and adult populations.

Super Refractory Status Epilepticus: either status epilepticus that is not controlled by a third line agent, or status epilepticus continuing for 24-hours or longer after third line medication.

(Nelson and Varelas, 2018)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Maintenance Dose</th>
<th>Serious Adverse Effects/Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg</td>
<td>0.05-2 mg/kg/h</td>
<td>Respiratory depression, hypotension, tachyphylaxis after long use</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>5-15 mg/kg</td>
<td>0.5-5 mg/kg/h</td>
<td>Cardiac and respiratory depression, hypotension, ileus, loss of neurologic examination at high doses</td>
</tr>
<tr>
<td>Thiopental</td>
<td>2-7 mg/kg</td>
<td>0.5-5 mg/kg/h</td>
<td>Cardiac and respiratory depression, hypotension</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.5-4.5 mg/kg</td>
<td>Up to 5 mg/kg/h</td>
<td>Hypertension, arrhythmia, anaphylaxis, pulmonary edema</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>Not established</td>
<td>End-tidal concentrations 0.8-2% titrated to EEG</td>
<td>Cardiac and respiratory depression, infections</td>
</tr>
</tbody>
</table>

(Nelson and Varelas, 2018)
Stage IV.II Super-refractory Status Epilepticus

- If seizures are still not controlled or recur, use one or more of the following alternative therapies:
  - Isoflurane or desflurane or gabapentin or levetiracetam (in acute intermittent porphyria)
  - Topiramate 300–1600 mg/d per orogastric tube (if no increased stomach residuals)
  - Magnesium 4 g bolus IV and 2–6 g/h infusion (keep serum levels <6 mEq/L)
  - Pyridoxine 100–600 mg/d IV or via orogastric tube
  - Methylprednisolone 1 g/d IV for 5 days, followed by prednisone 1 mg/kg/d orally for 1 week
  - IVig 0.4 g/kg/d IV for 5 days
  - Plasma exchange for 5 sessions
  - Ketogenic diet 4:1 (fat:carbohydrate and protein grams)
  - Neurosurgical resection of epileptogenic focus
  - Electroconvulsive therapy
  - Vagal nerve stimulation or deep brain stimulation or repetitive transcranial magnetic stimulation

(Nelson and Varelas, 2018)
Medication Management of Super Refractory Status Epilepticus
Any Questions?
References


Seattle Children’s

Hope. Care. Cure.”