Seizure Emergencies: Status Epilepticus

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Status Epilepticus

• Acute, life threatening neurological emergency
• Early identification and treatment is important as it can affect outcome and morbidity
• Incidence: Annual incidence of SE in the pediatric population ranges from 10 to 73 per 100,000
• The highest incidence is in children < 2 years (135 to 156 per 100,000) (Singh RK 2009)

Source:
Status Epilepticus - Definition

• Definition has evolved over the years
• Originally defined as “a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur” (ILAE 1981)
• Since then, SE defined as single seizure lasting >20-30 minutes, or
• Recurrent shorter seizures without recovery of consciousness between seizures
• Patients with a seizure lasting longer than 5 min (or 5–10 min in children) are now described as “threatened” or “impending” status epilepticus, and those that continue for longer than 30 min can be designated as established status epilepticus. (Freilich et al, Curr Opin Pediatr 2014)

Source:
Types of Status Epilepticus

- Generalized convulsive status epilepticus
- Focal motor status epilepticus with preserved awareness (*epilepsia partialis continua*)
- Non-convulsive status epilepticus (usually characterized by clinically subtle signs with altered awareness)
- Other seizures such as absence, myoclonic seizures can also present with prolonged seizures
Etiology of SE

- Broadly:
  - Acute Symptomatic
  - Remote Symptomatic
  - Idiopathic epilepsy related
  - Cryptogenic epilepsy related
  - Unclassified

Table 1. Common etiologies of status epilepticus in children and incidences from population-based studies

<table>
<thead>
<tr>
<th>Acute</th>
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<tbody>
<tr>
<td>Acute symptomatic (17%–52%)</td>
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<tr>
<td>Acute CNS infection (bacterial meningitis, viral meningitis, encephalitis)</td>
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<tr>
<td>Metabolic derangement (hypoglycemia, hyperglycemia, hyponatremia, hypocalcemia, anoxic injury)</td>
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<td>AED noncompliance or withdrawal</td>
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<td>AED overdose</td>
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<tr>
<td>Non-AED/drug overdose</td>
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<tr>
<td>Prolonged febrile convulsion (23%–30%)</td>
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<tr>
<td>Influenza</td>
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<td>Exanthem subicum</td>
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<tr>
<th>Remote (16%–39%)</th>
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<tr>
<td>Cerebral migrational disorders (lissencephaly, schizencephaly)</td>
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<tr>
<td>Cerebral dysgenesis</td>
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<tr>
<td>Perinatal hypoxic-ischemic encephalopathy</td>
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<td>Progressive neurodegenerative disorders</td>
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<tr>
<th>Idiopathic/cryptogenic (5%–19%)</th>
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<tbody>
<tr>
<td>AED—antiepileptic drug; CNS—central nervous system.</td>
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</table>

Source:
RESCUE MEDICINE FOR EPILEPSY IN EDUCATION SETTINGS

Adam L. Hartman, Cynthia Di Laura Devore, and the SECTION ON NEUROLOGY, COUNCIL ON SCHOOL HEALTH
Pediatrics; January 2016, Volume 137/ Issue 1
School Action Plans for CYE

• School Nurses
  • Rely on prescribing professionals for medical orders to manage CYE patients in school
  • Based on medical orders, effective action plans are written for use by unlicensed assistive personnel

• Where there are no school nurses, action plans are provided by prescribing professionals
  • Prescribing professionals may create an action plan or modify a generic form
  • Ex: www.epilepsyfoundation.org

• Additional links to epilepsy in school can be found at American Academy of Pediatrics Council on School Health (www2.aap.org/sections/schoolhealth, under resources)
Factors to consider when writing a seizure action plan

- Seizure rescue medications are given once a seizure has lasted 5 minutes to prevent progression to SE
- Can modified on the basis of observations made by those caring for the CYE patient at home and school
  - Ex: some patients have short seizures, if allowed to continue for longer than 1 minute, will result in SE. In this case, the provider may prescribe seizure rescue medications to be given as soon as the seizure begins.
- Account for concomitant medications and past reactions to different medicines
- Understanding of when a child is safe to remain in school after a seizure or when further medical care outside of the school setting is indicated

Rescue Medication Options
Treatment

• Acute treatment of seizures (often outside the ED):
  • Diazepam (rectal) Gel
  • Midazolam (intranasal or buccal)
  • Lorazepam (buccal or sublingual)
  • Clonazepam (oral)
Midazolam

- Increasingly used by emergency medical services because of its short elimination half-life (2.5 hours)
- Oral syrup (2mg/mL) is also available
- Can be used for buccal administration
  - With patient lying on his or her side provided patient does not have copious secretions or emesis during the seizure
- Some pharmacies have adapted the use of syringes to deliver the intravenous form of midazolam intranasally
  - Demonstrated to be more effective when administered by family caregivers
- Premeasured syringes may improve the safety of this medication in school settings
- If intranasal formulation is prescribed,
  - Additional training of school personnel may be considered due to new route of administration

Lorazepam

• Available as an oral solution (2mg/ml)
• Used for oral administration provided the patient does not have numerous secretion or emesis during the seizure
• Recommended that it be refrigerated, hence less practical outside of school
• Premeasured syringes may improve the safety of this medication in school settings
• Unlicensed assistive personnel typically not asked to administer unless provided a premeasured syringe

Clonazepam

- Available as an orally disintegrating tablet in different doses
- Prescribers may include:
  - Specific instructions about positioning a child on his or her side to drain secretions
  - How to safely position the medication into the buccal mucosa to avoid injury by a patient’s clenched teeth

• If seizures haven’t stopped with acute intervention in the field or in the ED....
Status Epilepticus

• Initial assessment and treatment
  • ABCs and glucose
  • History
  • Neurologic and general examinations
Status Epilepticus: 0-9 minutes

- Place IV and obtain blood for:
  - Glucose
  - Electrolytes
  - BUN
  - Calcium
  - Magnesium
  - CBCPD
  - AED levels, if relevant
  - Alcohol/Toxicology screen if relevant
- 100 mg thiamine, 25 g glucose
Status Epilepticus

- If seizures are still occurring:
  - Lorazepam
    - Preferred initial treatment
    - 0.05-0.1 mg/kg (maximum 2mg per dose)
    - Repeat as necessary, maximum of 0.3 mg/kg within 1 hour
  - Diazepam (0.25 mg/kg)
    - Used when oral administration of a seizure rescue medication may be contraindicated.
    - Faster onset but redistributed to fat quickly, so effective period only 15-30 minutes
    - Recurrent seizures more common
Status Epilepticus

• If seizures have not stopped
  • Phenytoin
    • 20 mg/kg at 50 mg/min (1 mg/kg/min in children) in Normal Saline
  • Fosphenytoin (*used more widely but more expensive*)
    • 20 mg/kg Phenytoin Equivalents at 100-150 mg/min (1-3 mg/kg/min in children)
  • Monitor BP (can cause hypotension), EKG (arrhythmias)
Status Epilepticus

• If seizures persist
  • Intubate or be ready to intubate
  • Phenobarbital 20 mg/kg at 100 mg/min IV
  • Or infusions (barbiturates, benzodiazepines)
Status Epilepticus: >1 hour

• EEG monitoring:
  • After initial treatment, seizures may persist on EEG, even if they have stopped clinically (electroclinical dissociation)
  • Treatment of SE should not be delayed for EEG

• Pentobarbital 5 mg/kg load, then 1-3 mg/kg/hour titrated to burst suppression

• Or…
  • Midazolam drip
  • Repeated phenobarbital boluses
  • General anesthesia
Refractory and Super Refractory SE

Table 2. Potential options for pharmacologic treatment of status epilepticus

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Rate Acute status epilepticus</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.1–0.15 mg/kg IV</td>
<td>&lt; 2 mg/min</td>
<td>Hypotension, respiratory depression, depressed level of consciousness</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.3 mg/kg IV, 0.5–0.7 mg/kg rectal</td>
<td>IV over 2–5 min to prevent apnea</td>
<td>Hypotension, respiratory depression, depressed level of consciousness</td>
</tr>
<tr>
<td>Phenytin</td>
<td>20 mg/kg up to 25 mg/kg IV</td>
<td>50 mg/min</td>
<td>Hypotension, cardiac arrhythmias</td>
</tr>
<tr>
<td>Phosphenytin</td>
<td>15–20 mg/kg up to 25 mg/kg PT IV</td>
<td>150 mg PE/min</td>
<td>Hypotension, cardiac arrhythmias</td>
</tr>
<tr>
<td>Phenybralbital</td>
<td>15–20 mg/kg up to 30 mg/kg or serum concentration 15–45 mg/L</td>
<td>1 mg/kg/min (maximum 2 mg/kg/min in child, 100 mg/min in adult)</td>
<td>Hypotension, respiratory depression, depressed level of consciousness</td>
</tr>
<tr>
<td>Valproate (remains experimental)</td>
<td>20 mg/kg IV then 1 mg/kg/h or 24 mg/kg divided every 8 h (maintain serum concentration at 7.5 mg/L, or &gt; 100 mg/d when dosing every 4 h)</td>
<td>6 mg/kg/min</td>
<td>Hypotension, fatal hepatotoxicity</td>
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Refractory status epilepticus

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Rate or to effect</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>0.01–0.1 mg/kg/min or to effect</td>
<td></td>
<td>Hypotension, respiratory depression, depressed level of consciousness</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.15–0.3 mg/kg load, 1–18 μg/kg/h or to effect</td>
<td></td>
<td>Respiratory depression (less common)</td>
</tr>
<tr>
<td>Phenybralbital (high dose)</td>
<td>Dosing twice daily to achieve increased serum concentration (up to 70 mg/L)</td>
<td>Respiratory depression but develop tolerance</td>
<td></td>
</tr>
<tr>
<td>Penobarbital</td>
<td>2–10 mg/kg load* up to 20 mg/kg! then 0.5–5 mg/kg/h or to effect</td>
<td>Cardiac suppression, hypotension, poor cardiac output, immune suppression, respiratory depression</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>3–5 mg/kg load then 1–4.5 mg/kg/h or to effect</td>
<td>Propofol infusion syndrome in children</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>20 mg/kg load then additional 20 mg/kg to effect or maximum of 80 mg/kg/d (500–3000 mg/d in adults)</td>
<td>Sedation, irritability</td>
<td></td>
</tr>
<tr>
<td>Topiramate (remains experimental)</td>
<td>2–5 mg/kg bolus NG to maximum of 20 mg/kg/d or to effect (300–1600 mg/d in adults)</td>
<td>Metabolic acidosis</td>
<td></td>
</tr>
</tbody>
</table>

*Rate is over 1 hour.
†Rate is over 2 hours.
IV—intravenous; NG—naso gastric; PE—phenytin equivalent.

Source:
Adverse Effects

• Decreased respirations
• Oversedation
• Cardiopulmonary instability
  • May vary in severity depending on the duration of the seizure
  • Dose of the seizure rescue medication
  • Interactions with other medicines

Complications

• Refractory and superrefactory status epilepticus
• Respiratory depression (from treatment)
• Metabolic acidosis
• Complications from drugs (hypotension etc), intubation, mechanical ventilation
Outcomes

• Exact incidence of secondary brain injury is not known

• Probably depends of etiology (underlying cause) of SE

• Possibly worse outcome with higher seizure burdens (as seen with continuous EEG studies)

• Electrographic SE may be associated with high mortality and worsened pediatric cerebral outcome (Topjian et al, Crit care med 2013)

Outcomes

• Long term study: 60 children with 2.7 year follow-up of PICU admission for SE showed that electrographic SE had unfavorable outcomes in Glasgow Outcome Scale, Pediatric QOL scores (Wagenman et al, Neurology 2014)

Source:
Febrile Status Epilepticus - Risk Factors

• Risk factors for febrile SE (compared with simple FS)
  • Younger age
  • Lower temperature
  • Longer duration of fever before SE
  • Females
  • Structural temporal lobe abnormalities, and
  • Family history (first-degree) of FS

Source: Hesdorffer DC, J Pediatrics 2013
Practical Issues in Educational Settings

• Prescribing professionals may provide guidance on:
  • Management of potential adverse effects of seizure medications, either outlined in
    • medical orders to a school nurse
    • in simple language of an action plan for unlicensed assistive personnel
  • Types of situations in which school personnel could seek further medical assistance
    • if the student’s seizure doesn’t stop
    • if there is a concern for further-seizure or treatment related complications
  • The availability of cardiopulmonary resuscitation-trained personnel is suggested during medical emergency

Practical Issues in Educational Settings

• Availability of school nurses
  • Not available in every jurisdiction
  • When available, may not always be immediately available to assist in the case of a seizure
    • Ex: In some areas, a single nurse may be assigned to a group of schools
    • The ability for the nurse to respond in a timely manner depends on factors such as,
      • Distances between school buildings
      • Nurse-to-student ratios
      • Available assistance within a school to leave the health office uncovered to respond to a child in need
  • When prescribing seizure rescue medications because administration by others may be illegal in some jurisdictions
    • In states with strict licensure laws, schools without school nurses might be required to hire a one-on-one private duty nurse.

Practical Issues in Educational Settings

- School settings encompasses not only the classroom, but also
  - Bus transportation
  - Activities before and after school
  - Off-campus activities, such as field trips and athletics

Legal considerations

- Recommended that providers who care for children with epilepsy be aware of local laws regarding administration of seizure rescue medications by school personnel and their personal liability for errors.
- If school transportation services are contracted out to private companies, it might raise additional potential liability issues whereby some private transportation companies may prohibit involvement of employees in the case of a medical emergency.

Key Points

• Prescribing professionals
  • Should familiarize themselves with the local and state regulations and local school limitation and resources for treating students with seizures
  • Should educate school personnel about seizure management or may direct them to educational programs offered by national or local organizations with appropriate expertise

• An individualized action plan will be more effective
  • Developed collaboratively among the family, the prescribing professional, and the school
  • Taking into consideration the possible options for the least restrictive medication choice for the child in his or her environment while ensuring the child’s safety
  • Include details of when to activate emergency medical services, depending on the patient and available resources
  • Included in the IEP or 504 accommodation

"Consequences of Prolonged Febrile Seizures in Childhood" (FEBSTAT) study

Design and phenomenology of the FEBSTAT study

*†Dale C. Hesdorffer, ‡¶Shlomo Shinnar, #Darrell V. Lewis, **Solomon L. Moshé, ††Douglas R. Nordli Jr, ‡‡¶¶John M. Pellock, #†James MacFall, ‡Ruth C. Shinnar, ‡David Masur, ***L. Matthew Frank, ††Leon G. Epstein, *Claire Litherland, ‡‡¶¶Syndi Seinfeld, †††Jacqueline A. Bello, †††Stephen Chan, §§¶Emilia Bagiella, ¶¶¶Shumei Sun, and the FEBSTAT study team

Source:
- Design and phenomenology of the FEBSTAT study. Hesdorffer DC et al, Epilepsia 2012
FEBSTAT

- Prospective, multicenter study.
- Children, aged 1 month to 6 years of age.
- Febrile seizure lasting 30 min or > based on ambulance, emergency department, and hospital records, and parental interview.
- Baseline information: H&P, MRI and EEG within 72 hours of febrile SE.
FEBSTAT Management Outcomes

- Included 199 children 1 month to 6 years in age
- Febrile SE: FS > 30 mins duration
- 170 children received at least one AED to stop febrile SE, > 1 drug needed in 140 patients
- Median time to receiving first AED was 30 mins
- Median time from the first dose of AED to end of seizure was 38 min
- Mean seizure duration was 81 min for subjects given medication prior to ED and 95 min for those who did not (p = 0.1).
- Reducing the time from seizure onset to AED initiation was related to shorter seizure duration

Source:
- Shinnar S, Epilepsia 2014