



## **Pediatric Seizure and Status Epilepticus (SE): A Primer for Treating Challenging Pediatric Seizure Cases**

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### **Introduction**

A 9 month old has a prolonged seizure but has no IV access. What do you do?

A 7 year old has repeated staring episodes with tachypnea and tachycardia.  
What is your working diagnosis? How do you treat this patient?

A 12 year old autistic child on po Depakote has two seizures on the school bus.  
What work-up is required? How can the valproate level be restored in the ED?

A 21 year old has a first time seizure after cramming for exams and then partying.  
What is the likely diagnosis? How should this patient be treated?

A 13 year old is seen at home thrashing in the bed, but does not have a seizure.  
Is this really a seizure? What work-up would you do in the ED?

This document addresses pediatric seizures and SE so as to optimize the outcome of these patients when treated in the Emergency Department.

## **Overall Seizure Epidemiology**

There are an estimated 2.5 million patients with epilepsy in the United States, a prevalence of about 6.6 per 1000 Americans. Up to 28% of these epilepsy patients are treated in the Emergency Department annually. Status epilepticus (SE) occurs in 50-150,000 patients per year, with a mortality of 22%. The incidence of SE is 50 per 100,000 Americans, with the greatest incidence being at the extremes of age. Status epilepticus is seen in up to 7% of Emergency Department seizure patients, and most emergency physicians report treating five or more cases of SE per year. The etiology of SE in the Emergency Department is similar to that of all emergency seizure patients, with alcohol, drugs, or low anti-epileptic drug (AED) levels causing more than 50% of SE episodes treated.

## **Pediatric Seizure Epidemiology and Etiology**

The CNS of children is more immature, making children more likely to seize but also more refractory to the consequences of an acute seizure or SE. SE is most common in children younger than one year of age and in children who develop SE, 50% will do so in the first year of their life. The most common causes of SE in children are fever, CNS infection, and epilepsy, accounting for over 75% of SE episodes in children less than one year of age. Other etiologies of SE in children include hyponatremia, inadvertent ingestions of cocaine or other toxins, and structural CNS abnormalities. The outcome of children with SE depends on the CNS status of the child prior to the onset of the SE; the better outcomes associated with children without underlying CNS abnormalities. The 3-6% mortality seen in pediatric SE most often is related to an acute neurological insult or a chronic CNS condition.

In two studies from an urban ED, up to one percent of all patients seen in the ED were noted to be pediatric seizure patients. Febrile seizures were noted to comprise 80% of these patients, with only 20% of pediatric patients presenting with afebrile seizures. Febrile seizures are commonly seen in the emergency department because they occur in 2-5% of all children. By definition, simple febrile seizures are brief (lasting less than 15 min duration), generalized, and non-recurrent. Given the more aggressive definition of SE being used today, it is reasonable to consider children whose febrile seizures last for greater than 5-10 minutes to be complex, and diagnose the patient as having SE.

## **Seizure Classification**

Pediatric seizures can be broadly classified into generalized and partial seizures. Generalized seizures involve both cerebral hemispheres, while partial seizures involve only one cerebral hemisphere. Generalized seizures either are convulsive (generalized tonic-clonic seizures) or non-convulsive (absence seizures). Partial seizures are either simple, in that they do not involve an alteration in consciousness, or complex, when there is impaired consciousness.

Simple partial seizures manifest themselves based on the location of the seizure focus, and can have focal motor movements, sensory, autonomic, or somatosensory symptoms. When partial seizures are complex, they most often involve the temporal lobe, and cause cognitive and affective abnormalities, and psychomotor seizures.

Other generalized seizure types in children include neonatal seizures, benign childhood epilepsy, infantile spasms, Lennox-Gastaut syndrome, atonic seizures, and febrile seizures. These seizure types are more fully addressed in the slide presentation.

Status epilepticus can be divided into convulsive, non-convulsive, and subtle SE. Convulsive SE describes a generalized seizure that lasts greater than 5-10 minutes. This more aggressive SE definition shortens the seizure duration criteria from 30 minutes, and is consistent with the treatment philosophy that prompts paramedics, nurses and emergency physicians to treat seizures early, regardless of duration.

Non-convulsive SE includes a prolonged absence or complex partial seizure. Complex partial SE may be present in a patient with waxing and waning mental status and/or intermittent bizarre or unusual behavior. Complex partial SE patients may also develop generalized seizures after they present to the Emergency Department. Subtle status epilepticus, which is a late manifestation of prolonged SE and is a sign of profound encephalopathy, may be the diagnosis in frankly comatose patients who have only minimal focal motor activity. In the past, a patient with subtle SE may have been considered less sick than a patient with generalized convulsive SE (GCSE) because of the absence of generalized seizure activity. Up to 20% of comatose patients whose generalized seizures have been terminated may continue to have ictal discharges on EEG. The absence of clinical manifestations of SE leads to the designation "subtle SE". Patients who present with or develop subtle SE are usually elderly patients with significant co-

morbidities and are more refractory to initial therapies, causing a higher mortality rate, up to 50% at 30 days. This type of SE is not likely to be observed in the pediatric population unless there is a profound chronic underlying CNS condition.

## **Pre-hospital Pediatric Seizure Therapy**

The pre-hospital treatment of pediatric SE with diazepam has been shown to reduce seizure duration by 47% and to reduce the seizure recurrence rate by 32%. The Chicago EMS seizure SMOs allow for multiple 0.1 mg/kg doses of diazepam in children prior to transport. Rectal diazepam, dosed at 0.3-0.5 mg/kg, has been shown to be safe and effective in seizing children when IV diazepam cannot be given, and is often listed as a SMO alternative when IV access is not available. Midazolam is now being used more often in EMS SMOs, since it can be used effectively via both the IV and IM routes, precluding the need for diazepam, which requires rectal use when IV access is not possible. EMS systems that utilize midazolam recommend multiple 0.1 mg/kg doses in children.

## **Emergency Department Evaluation**

A complete laboratory evaluation may only be required in patients with complicated or new-onset seizures, those in SE, or in patients with significant comorbidity and/or at the extremes of age. One study of pediatric seizure patients established that the need for routine chemistry testing was not justified, given the low frequency of lab abnormalities. The only significant lab abnormality that has been noted is hypoglycemia, seen in up to 2% of seizing patients.

In patients who seize for prolonged periods, up to 50% may present with a temperature above 100.5, suggesting infection as the seizure etiology and prompting a lumbar puncture (LP) to be considered. Fever, leukocytosis, and CSF pleocytosis may accompany SE even in the absence of a CNS infection, complicating the ability to determine the etiology of a prolonged seizure.

In children, fevers commonly cause seizures and SE, despite the absence of meningitis. With the use of the HIB vaccine, the risk of meningitis is greatly reduced, making meningitis as a possible cause of a prolonged febrile seizure less likely. One study demonstrated that a simple febrile seizure was never the sole finding in a pediatric patient with meningitis.

The published AAP guidelines that discuss the management of children with febrile seizures, allow for the Emergency Physician to defer most diagnostic tests, including lumbar puncture, except when clinically indicated. This is appropriate given the diminished possibility of CNS Haemophilus influenzae b infection in children who have been HIB vaccinated, since it had been the most common cause of meningitis in children in the age group associated with febrile seizures. The current ACEP guidelines also suggest that an LP is only required in the presence of immunocompromise, meningeal signs, persistent AMS, or a clinical history suggestive of a CNS infection.

Neuroimaging is indicated for seizures that are new-onset, complicated (including SE), and in patients with co-morbid conditions that impart a greater risk of complications. A non-contrast head CT performed in the Emergency Department is a reasonable first imaging study, since it may diagnose space occupying lesions, mass effect, trauma, hemorrhage, and/or cerebrovascular infarcts. Contrast-enhanced CT might only be necessary after the initial non-contrast CT suggests a space occupying lesion that is better diagnosed using contrast, such as a CNS tumor or an isodense subdural hematoma, for example. One study has demonstrated that children with complex febrile seizures, a normal neurologic exam, and afebrile seizure patients without a clear acute cause evident on history and physical rarely have a positive CT, such that this test can be deferred if appropriate follow-up can be arranged.

The use of electroencephalography (EEG) in the Emergency Department has been limited, despite its ability to diagnose subtle SE in seizure patients who remain comatose for prolonged periods after the termination of a generalized seizure. Only 12% of emergency physicians report having access to EEG in the Emergency Department, and only 15% have used it in the evaluation of suspected subtle SE. An EEG should be considered whenever subtle SE or complex partial SE is suspected, as well as in patients who require neuromuscular paralysis, intubation, pentobarbital, and/or general anesthesia for seizure control. For example, if a child remains comatose for more than 30-40 minutes after resolution of a prolonged seizure, an EEG might be useful in detecting an ongoing seizure focus or SE. The EEG could be performed upon arrival in the pediatric ICU if this test is not routinely available in the ED.

Two channel EEG monitors are available for use with Emergency Department cardiac monitors that include changeable modular ports. This technology could allow the emergency physician to quickly determine if persistent seizure activity is

taking place, so that additional therapy or consultation can take place prior to ICU disposition.

## **Pediatric Seizure and SE ED Therapy**

Recommendations regarding the treatment of SE, published by the Working Group on Status Epilepticus, provide the basis for optimal SE management in the Emergency Department. Although these guidelines are not specific for pediatric patients, they do outline an initial diagnostic and treatment paradigm, including the time course over which drug therapies should be provided. Important aspects of this treatment guideline for emergency physicians include the rapid implementation of an established treatment protocol, adequate dosing on a mg/kg basis, so that refractory SE can be treated as quickly as possible.

There are many standard and new therapies available to assist the emergency physician in terminating seizures and SE. Most uncomplicated seizure patients, including those who develop SE, will respond to initial drug therapies in about 80% of cases. More than the use of a specific drug, the most important factors in seizure termination are the rapid use of effective drugs in adequate doses, based on estimated weights and mg/kg requirements. Therapy can be optimized, therefore, by the development of guidelines that include rational, sequential drug therapy that mandates appropriate dosing prior to considering any individual AED to be ineffective.

Benzodiazepines, which work through the GABA inhibition of repetitive firing, are easy to use, rapid acting, with efficacy of at least 79% in the treatment of SE. Alternate benzodiazepine administration routes include intramuscular (IM), intranasal, and buccal midazolam, as well as rectal emulsified diazepam. When administered IM, midazolam only takes 116 seconds to terminate seizures, as compared to 34 seconds when given by the intravenous (IV) route. Intranasal and buccal midazolam have also been shown to be as effective as diazepam in randomized, controlled clinical trials. The new form of rectal diazepam, called Diastat, comes pre-packaged as an emulsion that can be given rectally without the need to draw up the diazepam in a tuberculin syringe or to tape or hold the buttocks together while the drug is being absorbed. At a minimum, these alternate benzodiazepine routes should make it unnecessary to infuse AEDs via the interosseous route.

Phenytoins work through membrane  $\text{Na}^+$  and  $\text{Ca}^+$  channel stabilization, reducing the likelihood of repetitive neuronal firing. The standard phenytoin dose of 18-20

mg/kg is rarely exceeded in the treatment of SE, even though high dose (30 mg/kg) phenytoin therapy is recommended for SE refractory to standard phenytoin loading doses. Fosphenytoin, the water-soluble pro-drug of phenytoin, is dosed in phenytoin equivalents, making dosing comparable to that of phenytoin. It can be infused more rapidly than phenytoin with less pain, fewer injection site reactions, and fewer adverse events. A loading dose of fosphenytoin can be given IM with therapeutic phenytoin within 20-30 minutes.

Barbiturates are an effective class of AEDs that work through the enhancement of GABA inhibition of neuronal firing. Although phenobarbital effectively treats seizures and SE, its formulation, administration difficulties, and long half-life all limit its usefulness in the Emergency Department. Pentobarbital, when used as an anesthetic in the treatment of refractory SE, requires airway management, extensive cardiovascular and EEG monitoring, and neurological consultation.

IV valproate is also available for use in Emergency Department seizure patients who require rapid therapeutic drug level restoration. This drug can be loaded in doses of 25-30 mg/kg at rates up to 3-6 mg/kg/min (to a maximum rate of 300 mg/min) in children as young as 2-3 months of age without significant complications. Because many of the seizure etiologies in children warrant long-term PO divalproex therapy, it is reasonable to load pediatric patients who require protection from or therapy for SE with IV valproate.

There have been case reports of the use of lidocaine in the treatment of seizing patients who are refractory to conventional therapies. Because this Na<sup>+</sup> channel drug is not likely to terminate most cases of SE, it should not be considered to be a useful adjunctive therapy when initial therapies fail to terminate SE.

Refractory SE, defined as SE non-responsive to initial therapy with benzodiazepines, phenytoins, phenobarbital, and valproate, occurs in up to 22,000 patients per year. In a case report of an actively seizing pediatric patient, propofol was successfully used to treat the refractory SE. It is an anesthetic agent that may be used to treat SE because it provides burst suppression through GABA inhibition. Besides pentobarbital and propofol, midazolam can be given as constant IV infusion for refractory SE, or inhalation anesthetics can be used to achieve EEG burst-suppression.

## **Special Considerations in Pediatric Seizures and SE**

In pediatric head trauma patients, it has been shown that patients with a GCS of 3-8 are at greatest risk for developing seizures. Although long-term seizures are not prevented through the prophylactic use of AEDs such as phenytoin or valproate in these patients, the occurrence of early seizures (during the acute hospitalization) can be prevented with seizure prophylaxis.

As was stated previously, many of the seizure etiologies that cause seizures and SE in children and adolescents can be optimally treated long term with PO divalproex. It is reasonable, therefore, to consider IV valproate as one of the initial therapies to be used when treating pediatric patients. One specific seizure etiology that highlights this treatment guideline is juvenile myoclonic epilepsy (JME). College students who are often sleep deprived and who have ingested alcohol, may present with an early morning generalized seizure. These patients might have a history consistent with absence seizures as a child, but no specific work-up or seizure therapy. In these patients, valproate is the optimal drug to be used if an ED load is required, since phenytoin can, in fact, worsen the symptoms of JME when it is used long term.

## **Conclusions**

Pediatric seizures and SE are neurological emergencies that require prompt and effective treatment by emergency care providers. Outcome can be enhanced for all of these patients by providing consistent care that follows a protocol, using effective drugs in adequate doses. Future research will continue to establish how pediatric patient outcome can be improved through better use of current treatment modalities and the development of new therapies that can be effectively used in the emergency setting.