Shake, Rattle, and Roll An Update on Pediatric Seizures

Sarah Szlam, MD and Mark Meredith, MD

Abstract: Seizure is a common presenting complaint for patients in the pediatric emergency department (PED) setting. In some cases, protocols are in place on how to manage this group of patients, for example, a patient with a simple febrile seizure already back to baseline or a patient with known epilepsy already back to baseline. However, many scenarios present dilemmas for physicians in the PED, specifically patients with status epilepticus (SE). Unfortunately, there is not a national SE protocol, and hospital-specific guidelines may or may not exist. Current practices are constantly changing because new medications arise, and more information is gathered regarding existing medications and guidelines. Here we will review the basics about first-time afebrile seizures presenting to the PED and common treatments specific to seizure types. We will then review SE management basics and medical therapy, including both older and newer agents and their routes of administration for both the prehospital and the hospital setting.

Key Words: seizure, status epilepticus

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TARGET AUDIENCE

This article is intended for Emergency Medical Technician/ paramedics, emergency and pediatric emergency medicine physicians, nursing, and nurse practitioners.

LEARNING OBJECTIVES

- After completion of this article, the reader should be able to:
- 1. Define and diagnose common pediatric seizure types, presentations, and treatments.
- Implement appropriate treatment of seizure activity and SE starting with the Airway, Breathing, and Circulation and including medication options, algorithms, and modes of administration.

Seizure is a common presenting complaint for patients in the pediatric emergency department (PED) setting. In some cases, protocols are in place on how to manage this group of patients, for example, a patient with a simple febrile seizure already back to baseline or a patient with known epilepsy already back to baseline. However, many scenarios present dilemmas for physicians in the PED, specifically patients with SE. Unfortunately, there is

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Copyright © 2013 by Lippincott Williams & Wilkins ISSN: 0749-5161 not a national SE protocol, and hospital-specific guidelines may or may not exist. Current practices are constantly changing because new medications arise, and more information is gathered regarding existing medications and guidelines. Here we will review the basics about first-time afebrile seizures presenting to the PED and common treatments specific to seizure types. We will then review SE management basics and medical therapy, including both older and newer agents and their routes of administration for both the prehospital and the hospital setting.

FIRST-TIME AFEBRILE SEIZURE IN THE PED

When a seizing patient arrives to the emergency department (ED) with no history of seizures, the history, physical assessment, and age of the child can be quite helpful in determining what steps, if any, to take next. The initial physical examination should ensure that the ABCs are intact. The child may be sleepy and in a postictal state but should be responsive. If the initial findings and cursory history are concerning, the provider may need to obtain laboratory tests and imaging before obtaining a detailed history. These are cases where there may be a concern for nonaccidental trauma, intracranial hemorrhage, ingestions, stroke, meningitis, cardiac dysrhythmia, or other more serious conditions that require rapid diagnosis and treatment.

In cases where the patient is stable, the physician should get a very thorough history from the patient (if possible) and the family. The family should be asked about events preceding the seizure and a description of the seizure, including loss of consciousness, duration, focality versus generalized, progression of the seizure, cyanosis, bowel or bladder incontinence, length of the postictal state, characteristics of the postictal state, and any neurologic changes after the event. The family should provide any information on recent medication changes, possible ingestions, recent illnesses, immunizations, significant medical problems for the patient, and pertinent family history. The family should specifically be asked about seizure disorders, bleeding disorders (including venous malformations), and sudden cardiac death in any family members. If the patient is an infant, a prenatal and birth history should also be obtained. Of note, in patients with known seizure disorders, one should ask about current medications, recent changes, compliance, and any new medications that could potentially interfere with antiepileptics.¹

Once the history is obtained, a thorough physical examination should be performed. The patient's vital signs should be evaluated for any abnormalities that may suggest a potential cause of the seizure. For example, an abnormal heart rate in an older child may make the provider think of toxidromes related to ingestions. The skin should be examined for any rashes or markings that suggest infection or underlying syndrome such as neurofibromatosis. The neurologic examination is obviously highly important in these patients. If the patient is postictal at the time of initial examination, the provider should be sure to obtain a repeat examination, however, to the best of the provider's ability, should be performed regardless of the patient's current state because it may reveal important findings. In infants, special

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attention should be paid to the head looking at head circumference and feeling the anterior fontanel. Developmental milestones should be evaluated as well, and parents should be asked about these and any missed milestones, delays, or regression.¹

The workup in children with a first-time afebrile seizure is dependent on the age of the child, history, and clinical examination. At a minimum, a bedside blood glucose and electrocardiogram, with particular attention to QT interval, should be obtained and may be all that is needed.^{1,2} Laboratory analysis on children older than the age of 6 months may not be needed unless warranted by the history and physical examination. In children younger than 6 months (and possibly younger than 1 year), along with the glucose level, basic electrolytes and a venous blood gas should be checked given the possibility of an underlying metabolic disorder. In children younger than 6 months, a sepsis cworkup, including lumbar puncture, should be strongly considered.¹

In older children, laboratory analysis and possibly a lumbar puncture should be guided by history and physical examination. A child with a history of vomiting, diarrhea, and signs of dehydration should have the electrolytes checked. A patient who fails to return to baseline mental status should have a venous blood gas, basic laboratory tests (including complete blood cell count and complete metabolic panel), blood culture, and head computed tomography scan followed by a lumbar puncture with cerebrospinal fluid analysis. In these patients, meningitis should be high on the differential diagnosis.^{1,2} In patients where there is concern for a toxidrome exposure or ingestion, venous blood gas, electrolytes, and toxic metabolite levels should be evaluated.^{1,2} For patients with bleeding disorder or in a state of altered coagulability, such as an oncology patient, coagulation factors should be checked, and the patient may need a head computed tomography scan. Finally, in those patients with prolonged seizures and a need for ongoing medical intervention, further workup is generally indicated with particular attention for possible nonaccidental trauma.1

Emergent imaging studies should be obtained in all infants (generally younger than 6 months but may consider younger than 1 year), patients with focal seizures, and patients who are in or remain in SE. Emergent imaging should also be highly considered in any patient with a bleeding disorder, sickle cell disease, malignancy, immunocompromised state, ventriculoperitoneal shunt, or neurocutaneous disorder.¹ Electroencephalogram is rarely indicated in the ED.^{1,2}

In patients with brief afebrile seizures that have ceased, anticonvulsant medicines will not be indicated. If the patient arrives seizing or has seizures while being evaluated in the ED, the use of antiepileptic medication should follow. These medications are described in later sections. Outpatient anticonvulsant therapy is generally not indicated in the case of a first-time unprovoked seizure. Patients should be instructed to follow up with a pediatric neurologist for further workup and for the decision to start medication.¹ It is also important that patients and families are counseled about safety, particularly regarding swimming, bathing, and driving.

COMMON OUTPATIENT MEDICAL THERAPIES BASED ON SEIZURE TYPE

Infantile Spasms

Also known as the West syndrome, seizure activity usually presents itself between the ages 4 and 18 months. It is typically seen in males more than in females and is more common in patients with tuberous sclerosis. It is associated with children with mental retardation. The episodes usually occur during sleep and are seen as a pattern of hypsarrhythmia on EEG. Treatment is with adrenocorticotropic hormone, prednisone, vigabatrin, and/or pyridoxine. Other newer agents have also shown some effectiveness.¹

Lennox-Gastaut

This seizure disorder typically presents in children ages 3 to 5 years and is associated with mental retardation as well. Seizures may be difficult to manage, but valproic acid is often used. These patients are often tried on a ketogenic diet with some relief.¹

Benign Rolandic Epilepsy

Children present with this nighttime seizure disorder between the ages of 3 and 13 years. In general, medication is not necessary unless the seizures are severe or frequent. If indicated, carbamazepine or levetiracetam are often used. Most children will outgrow these seizures.¹

Absence

Absence seizures are seen in children older than the age of 5 years. These seizures are short in duration, are characterized by a blank staring episode, and can usually be effectively treated with valproate or ethosuximide.¹

Juvenile Myoclonic Epilepsy of Janz

This seizure disorder usually presents in early adolescence and may be characterized by myoclonic jerks, tonic-clonic episodes, or absence seizures. It is usually treated with valproic acid or levetiracetam.¹

Status Epilepticus

The diagnosis of SE had been historically defined as a seizure lasting longer than 30 minutes without return to baseline. However, recently SE has been defined as seizure activity lasting for more than 5 minutes because recognition of medication delay increases the likelihood of refractory SE (RSE). Refractory SE is defined as a seizure lasting for more than 60 minutes and/or seizure that persists despite 2 to 3 antiepileptic medications given at adequate doses.^{3,4} Refractory SE occurs in approximately 9% of children in SE.³

When a patient arrives seizing, prompt management is essential (Fig. 1). As with every patient arriving to the ED, verification and establishment of the ABCs is the initial component of management. All patients should be placed on supplemental oxygen while seizing. If available, oral/nasal continuous end-tidal CO₂ monitoring can be used to monitor the respiratory effort and assess adequacy of ventilations.5 This monitoring should be continued, if available, in cases where the patient is intubated. If the patient is able to protect the airway initially, close monitoring with constant reevaluation of the ABCs is essential because the patient's status and needs may change. If the patient is unable to protect the airway, an artificial airway should be established. Medications needed for intubation should include anticonvulsant agents and are discussed in a later section. If the patient is intubated, paralytic agents and other medications used to keep the patient sedated may mask seizure activity. Thus, intubated patients should be placed on continuous EEG monitoring when admitted.² After the ABCs are established, the blood glucose level should be checked at a minimum.

Initial treatment of the seizure is dependent on many factors, including the patient's history, etiology of the seizure (head injury, hypoglycemia), type of access available, and so on. In general, benzodiazepines (BZD) are first-line therapy for all seizures. Benzodiazepines are fast acting and can provide rapid cessation of seizure activity. After BZDs, second-line therapy is often

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Management of Status Epilepticus

FIGURE 1. Management of status epilepticus. INH indicates isoniazid.

administered after the delivery of the BZD either to attempt to stop continued seizure activity or as a maintenance medication. Agents such as phenobarbital, phenytoin, and fosphenytoin are commonly used. Also in this category are pentobarbital and newer medications, including valproate and levetiracetam. Each of these second-line agents is usually given as an initial loading dose followed by a continuous infusion. Lastly, in patients who are on current isoniazid treatment or who are younger than 2 years, particularly neonates, pyridoxine should be considered.⁴ Each of these agents has its benefits and risks, which are discussed in the following section.

ANTICONVULSANT AGENTS

Older Agents

Initial Therapy—Benzodiazepines

Benzodiazepines are generally accepted as first-line therapy for SE. They are relatively safe and offer several modes of administration. Adverse effects include sedation, respiratory depression, cardiac dysrhythmia, and ataxia. Because of their mechanism of action, they are very effective against a variety of seizure types and have a rapid onset once they reach the brain. Studies have shown that their effectiveness is inversely related to the duration of seizure activity. Thus, administration earlier in SE is now being advocated.⁶

**if refractory seizures

Midazolam

Midazolam is 1 of the preferred first-line therapies for SE, especially if intravenous (IV) access is available.⁷ It is a convenient agent because it is available in multiple forms including IV, intramuscular (IM), buccal, and intranasal. It is also the BZD with the shortest time to therapeutic effect and the shortest half-life. It may be given in individual doses and given via infusion when IV access is available. Standard dosing is 0.1 to 0.3 mg/kg IV/IM/intraosseous (IO) (maximum, 4 mg).

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Infusion rates start at 1 μ g/kg per minute. Buccal and intranasal forms are given at doses 0.2 to 0.5 mg/kg (maximum, 10 mg).

Lorazepam

Lorazepam is also a preferred agent, especially when IV access is available.⁷ It has an onset time and duration of action (on/off) that falls between midazolam and diazepam. Lorazepam is available in IV and IM form, although IV is preferred. Standard dosing is 0.05 to 0.1 mg/kg IV/IM/IO (maximum, 5 mg) and is to be given over 1 minute.

Diazepam

Diazepam has the longest time to on/off. Although it is also available in IV form, it has not been found to be as effective as the other agents listed. It is, however, often prescribed for home use as an abortive agent in its rectal form. Standard dosing is 0.2 to 0.5 mg/kg IV/IM/IO (maximum, 10 mg) over 2 to 5 minutes. Rectal gel is dosed based on age (2–5 years, 0.5 mg/kg; 6–11 years, 0.3 mg/kg; >12 years, 0.2 mg/kg; maximum, 20 mg).

Second-Line Therapy

Phenytoin and Fosphenytoin

Both medications have been shown to be effective in treating SE. Fosphenytoin must be converted into free phenytoin, but it may be administered at a much more rapid rate; thus, both medications ultimately reach the brain in about 15 minutes. There is little evidence to show that 1 medication is more effective than the other; however, there are fewer risks associated with fosphenytoin.⁶ Both drugs are associated with potential cardiac dysrhythmias, although rare, and usually occur with more rapid administration.⁷ Phenytoin is more associated with local skin necrosis or purple glove syndrome and thus should be given at a slower rate than fosphenytoin and through a large-bore IV.^{2,6,7} Hypotension may be seen with both medications but again is more common with phenytoin especially with faster infusion rates. Phenytoin is available in IV form, whereas fosphenytoin is available in IV and IM forms. Dosing for phenytoin is 20 to 30 mg/kg IV/IO with an infusion rate of 1 mg/kg per minute (maximum, 50 mg/min). Fosphenytoin is dosed in phenytoin equivalents (PEs), and dosing is 20 to 30 mg PE/kg IV/IO (10-20 mg PE/kg IM) with an infusion rate of 3 mg PE/kg per minute (maximum, 150 mg PE/min).^{6,7}

Phenobarbital

Phenobarbital is often considered earlier in SE in infants and third-line therapy in older children. It works rapidly and effectively with a similar adverse effect profile to phenytoin and fosphenytoin. It does carry significant risk for sedation, respiratory depression, and hypotension, which may limit its use.^{6,7} Standard dosing is 20 mg/kg IV/IO with an infusion rate of 2 mg/kg (maximum, 60 mg/min).

Levetiracetam

Levetiracetam is becoming more widely used in SE. Although few studies looking at its use in comparison with that of other agents exist, it has been shown to be highly effective and safe in SE. It has a high termination rate for RSE. The adverse effect profile is relatively small, with a low risk of respiratory depression, sedation, or liver dysfunction. It is thus a good option for critically ill patients.^{6,7} However, it does rely on renal function, and thus, the dose should be adjusted if impairment

exists.⁷ Dosing is 20 to 40 mg/kg IV/IO with an infusion rate of 5 mg/kg per minute.

Valproate

Valproate has been shown to be highly effective in terminating both SE and RSE and has significantly less adverse effects in comparison with many of the other agents. It lacks the risks of hypotension and respiratory depression; however, it may cause thrombocytopenia or hepatotoxicity after the initial loading dose.^{7,8} Like levetiracetam, it works on a variety of seizure etiologies and at times when first-line therapies fail.⁷ Standard dosing is 30 to 40 mg/kg IV/IO with an infusion rate of 5 mg/kg per minute.

Pentobarbital

Pentobarbital is an older medication than valproate or levetiracetam for the control of seizures. It has been a treatment of choice for RSE because it works rapidly and has low incidence of treatment failure. However, it has a significant adverse effect profile, including a high frequency of hypotension, and is associated with respiratory depression and myocardial depression resulting in low cardiac output^{4,6} Standard dosing is 5 mg/kg IV/IO with an infusion rate of 1 to 3 mg/kg per hour.

Pyridoxine

Pyridoxine is specific to patients on isoniazid therapy, to those with pyridoxine deficiency, and in neonates. In children younger than 2 years with refractory seizures, pyridoxine may be considered because the medication may have been inadvertently discontinued in a patient with pyridoxine-controlled seizures.⁴ If this is suspected, patients should be given an IV/IO push of 50 to 100 mg. One to 5 doses may be needed for seizure activity to subside.^{1,4}

Newer Agents

Ketamine

Ketamine may be useful in RSE both for intubation purposes and to terminate seizure activity. Based on its mechanism of action as an N-methyl-D-aspartate receptor antagonist, ketamine is unlikely to be effective early in seizure activity.⁴ In patients where intubation is necessary for airway protection either due to seizure activity or due to medication administration resulting in respiratory depression, ketamine is a preferred agent. Caution should be used in patients with a possible head injury or increased intracranial pressure (ICP) because of the potential for increased ICP. However, newer literature did not find that ICP was significantly increased with ketamine administration.⁴ The adverse effect profile also includes hypotension, respiratory depression, and tachycardia.^{4,6} Standard dosing is 0.5 to 2 mg/kg IV/IO for a loading dose or intubation followed by a continuous infusion of 5 to 20 μ g/kg per minute.

Propofol

Propofol should also be considered in cases where intubation is necessary. It has a rapid onset and short half-life thus allowing for easy titration.⁴ However, its use in children is limited by the risk of propofol infusion syndrome (cardiac failure, rhabdomyolysis, metabolic acidosis, and renal failure, which may ultimately lead to death).^{4,6} The risk of infusion syndrome has been shown to be higher in patients with mitochondrial disorders, hypertriglyceridemia, or on a ketogenic diet.^{4,6} It also carries the adverse effects of hypotension and respiratory depression. Although it may be effective in treating RSE and helpful in cases where intubation is needed, its high risk profile without benefit in comparison with that of other agents limits its use in pediatrics. The standard dosing is 1 to 2 mg/kg IV/IO with an infusion rate of 2 to 5 mg/kg per hour.

CONCLUSIONS

Seizures and SE are common reasons for patients to present to the pediatric ED. Treatment is now being started earlier in the course of seizure activity as the definition of SE has evolved. Earlier treatment has been shown to help reduce the possibility of the seizure becoming refractory. This neurologic emergency requires effective treatment to help prevent RSE and potential morbidity and mortality. Providers should be aware of the multiple forms of medications that exist, as IV access may not always be readily available. Furthermore, because many of the antiepileptic medications carry the risk of respiratory depression and sedation, intubation supplies should be on hand, and close monitoring of cardiorespiratory status should be ongoing. In general, benzodiazepines are preferred for aborting seizure activity. If these fail or if longer-acting therapy is needed, second-line agents may be used, such as phenytoin, fosphenytoin, phenobarbital, valproate, and/or levetiracetum. Valproate and levetiracetum are becoming more widely used given their low adverse effect profile; however, research comparing their effectiveness with that of other agents is limited. Although a variety of medications exist, providers must use them appropriately according to their patient's medical condition while weighing the risks and benefits associated with each medication.

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CME EXAM

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CME EXAMINATION December 2013

Please mark your answers on the ANSWER SHEET.

Shake, Rattle, and Roll: An Update on Pediatric Seizures, Szlam and Meredith

- 1. Which agent/class of agents are considered the standard initial therapy?
 - a. Barbiturates
 - b. Benzodiazepines
 - c. Levetiracetam
 - d. Valproate
 - e. Phenytoin
- 2. Which of the following forms of midazolam is not available to treat pediatric patients with status epilepticus?
 - a. Buccal
 - b. Intranasal
 - c. Intramuscular
 - d. Intravenous
 - e. Rectal

- 3. A 2-month-old patient presents with seizures of unknown etiology. Patient has been treated with midazolam, phenytoin, and levetiracetam, and the seizure activity persists. Finger stick glucose level is normal. What should the next therapy be?
 - a. Ketamine
 - b. Propofol
 - c. Pyridoxine
 - d. Glucose
 - e. IV fluids
- 4. A reliable way to measure respiratory effort after seizure is oral/nasal end-tidal CO₂.
 - a. True
 - b. False
- 5. What seizure type commonly presents at nighttime?
 - a. Absence
 - b. Juvenile myoclonic epilepsy of Janz
 - c. Benign rolandic epilepsy
 - d. Infantile spasms

ANSWER SHEET FOR THE PEDIATRIC EMERGENCY CARE CME PROGRAM EXAM DECEMBER 2013

Please answer the questions on page 1292 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print):		
Street Address		
City/State/Zip		
Daytime Phone		
Specialty		
3. ABCDE		
4. (A) (B) (C) (D) (E)		
5. ABCDE		
Your completion of this activity includes evaluating them. Please respond to the following questions below.	1 2 3 4 5	
Was effective in meeting the educational objectives	$\begin{array}{c} 1 \\ \hline 0 \hline \hline 0 \\ \hline 0 \\ \hline 0 \hline 0$	
Was appropriately evidence-based Was relevant to my practice		
Please rate your ability to achieve the following objectives, both before this activity and after it:	Post	
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 Define and diagnose common pediatric seizure types, presentations, and treatments. UOOOO Implement appropriate treatment of seizure activity and SE starting with the Airway, OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO		
How many of your patients are likely to be impacted by what you learned from these activities? $\bigcirc <20\%$ $\bigcirc 20\%-40\%$ $\bigcirc 40\%-60\%$ $\bigcirc 60\%-80\%$ $\bigcirc >80\%$		
Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 – definitely will not change, 5 – definitely will change) How will you apply what you learned from these activities (mark all that apply):	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	
In diagnosing patients O In making treatment decisions O		
In monitoring patients O As a foundation to learn more O	~	
In educating students and colleagues () In educating patients and their caregivers	; ()	
As part of a quality or peformance improvement project () To confirm current practice ()		
For maintenance of board certification \bigcup For maintenance of licensure \bigcup		
10 consider enrolling patients in clinical trials \bigcirc		
Please list at least one strategy you learned from this activity that you will apply in practice.		
How committed are you to applying these activities to your practice in the ways	1 2 3 4 5	
vou indicated above? (1 – minimally, 5 – completely)	00000	
Did you receive any bias for or againts any commercial products or devices? Yes No	•	
If yes, please explain:		
How long did it take you to complete these activities? hours minutes		
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CME EXAM ANSWERS Answers for the Pediatric Emergency Care CME Program Exam

Below you will find the answers to the examination covering the review article in the July 2013 issue. All participants whose examinations were postmarked by October 14, 2013 and who achieved a score of 80% or greater will receive a certificate from Lippincott CME Institute, Inc.

EXAM ANSWER September 2013

1. C 2. E 3. E 4. A 5. E

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