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# Seizures in Children: Laboratory Diagnosis and Management

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**Author Disclosure**  
Dr Major did not disclose any financial relationships relevant to this article. Dr. Thiele disclosed that she is a consultant to Abbott Laboratories.

**Objectives** After completing this article, readers should be able to:

1. Formulate an appropriate diagnostic plan for a child who has seizures.
2. Discuss the management of epilepsy.

## Introduction

The initial article on seizures in childhood (October 2007) focused on the diagnosis and classification of seizures in children. This second article reviews investigational tools and management. The evaluation of a child who has a seizure disorder must be tailored to the findings on history and physical examination. The electroencephalogram (EEG) is the primary electrophysiologic tool; brain neuroimaging is the primary modality for evaluating neuroanatomic and functional features.

## Electrophysiology

The EEG can help confirm the clinical diagnosis of epilepsy, classify the type of epilepsy, localize the epileptic focus, and help determine if treatment can be discontinued safely. In general, 21 electrodes placed on specific locations on the patient's scalp measure voltage fluctuations of superficial neurons in relation to time. Figure 1 shows the position and labeling of the scalp electrodes; Figures 2 through 6 show examples of typical EEG tracings. Generalized epileptic syndromes are characterized by discharges recorded simultaneously at each electrode; partial epilepsy syndromes show localized spikes or slowing in the epileptogenic region. Epilepsy is a clinical diagnosis that cannot be made on the basis of abnormal EEG findings. In fact, EEG abnormalities can be found in 5% of children who have no history of seizures.

On the other hand, a normal EEG is noted in 10% to 20% of children who have epilepsy. EEG sensitivity can be enhanced by the use of activation methods such as hyperventilation, photic light stimulation, and sleep deprivation. Hyperventilation can trigger epileptic discharges in 80% of patients who have generalized absence epilepsy, and photic stimulation induces EEG abnormalities in up to 40% of patients who have generalized epilepsy. When the routine EEG appears normal but the clinical suspicion of epilepsy remains high, a sleep-deprived EEG sometimes demonstrates occult abnormalities.

Long-term video-EEG monitoring is indicated primarily if the diagnosis of epilepsy is in question or when the seizures are intractable to medical treatment. The goal of this technology is to record seizures to characterize the electrical pattern on EEG during the episodes, which often helps to pinpoint their origin. Video-EEG monitoring is essential for presurgical evaluation if surgical ablation of an epileptic focus is being considered. Video-EEG analysis is helpful to identify the nature of paroxysmal episodes, particularly in cases of pseudoseizures or nonepileptic events, frontal seizures, or paroxysmal movement disorders.

When more precise seizure focus localization is needed prior to resective epilepsy surgery, subdural grids or depth electrodes can be placed by a neurosurgeon. Subdural grids consist of strips of electrodes embedded in a flexible sheet of polyurethane compound. The grids are inserted surgically over suspected epileptogenic areas of the brain. Compared with standard EEG, subdural grids provide an electroencephalographic recording unaffected by artifacts and diffusion caused by the structures between the brain and the scalp. Each electrode in the grid also can be stimulated individually to delineate the

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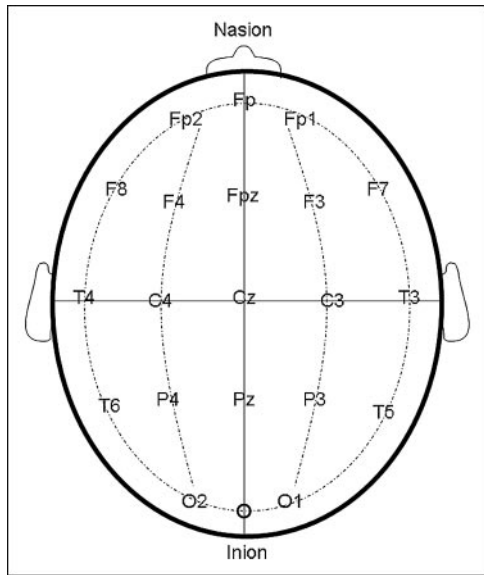


Figure 1. Scalp electrode positions for EEG. By convention, electrodes labeled with an even number are placed over the right hemisphere, and odd-numbered electrodes are placed over the left hemisphere. Fp=frontopolar, F=frontal, T=temporal, C=central, P=parietal, O=occipital, z=midline

“eloquent” brain regions (eg, hand area) that should be spared during epilepsy surgery. Depth electrodes allow recording of electrical activity coming from deep brain structures (eg, hippocampus).

### Brain Imaging

Computed tomography (CT) scan and magnetic resonance imaging (MRI) provide precise anatomic brain images and can identify potential epileptogenic lesions. Single-photon emission computed tomography (SPECT) scan, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) are functional brain imaging techniques that measure local vascular or metabolic changes associated with neuronal activity. Magnetic resonance spectroscopy is used in selected cases to measure local biochemical abnormalities.

The decision to order brain imaging and the choice between CT and MRI depend on the child’s clinical presentation and the availability of scans. Due to higher resolution, MRI is now the gold standard for the neuroimaging evaluation of epilepsy. Subtle lesions such as mesial temporal sclerosis, developmental brain malfor-

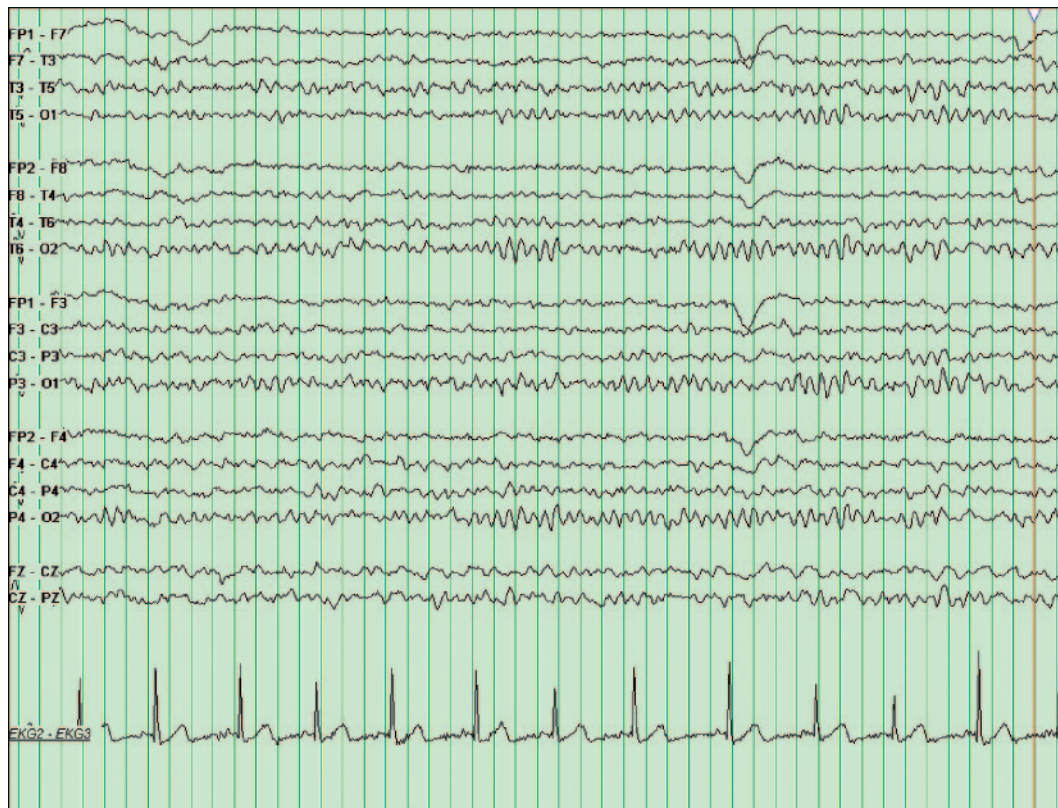


Figure 2. Normal EEG tracing showing a reactive posterior alpha (9-Hz) rhythm in an 8-year-old boy who has no history of seizures. The slow waves observed in the frontal areas are associated with eye movements.

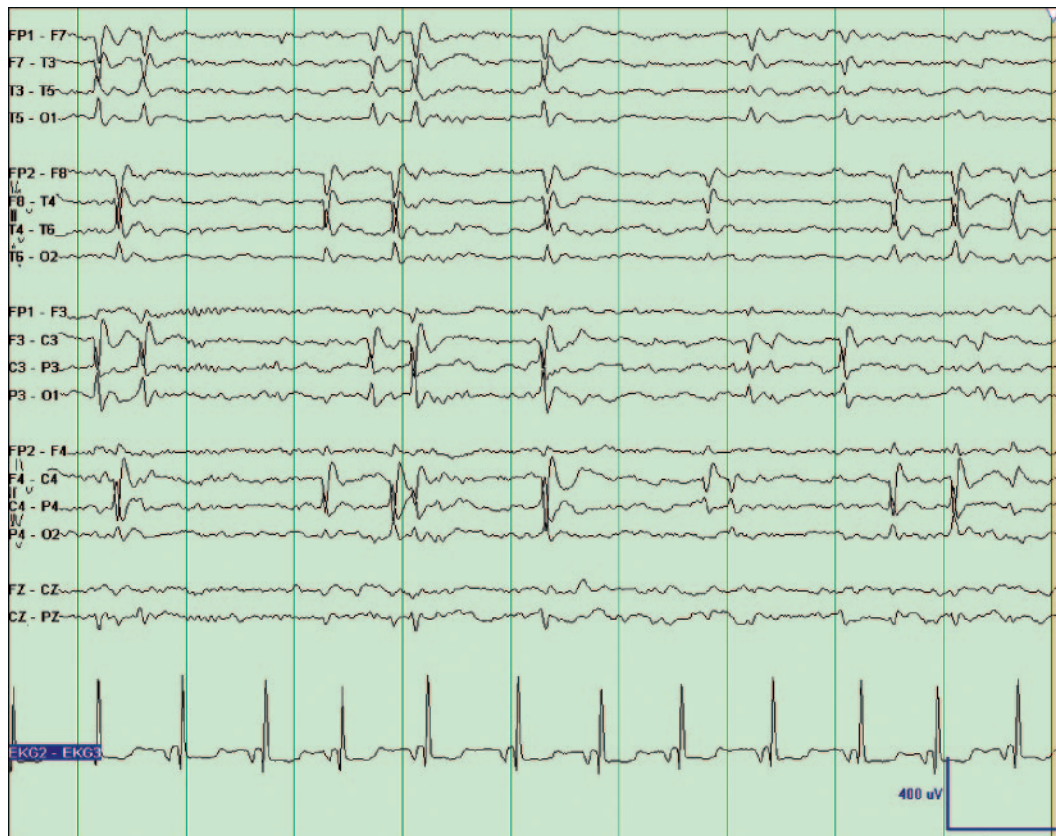


Figure 3. EEG tracing showing frequent independent left and right centrotemporal spikes in an 8-year-old child who has benign partial epilepsy with centrotemporal spikes (also called benign rolandic epilepsy).

mations, and arteriovenous malformations sometimes can be detected only on MRI. CT is reserved for cases when the MRI is not available. Although brain imaging is recommended for children who have focal-onset seizures, it is not necessary for normally developing children who have generalized seizures or typical febrile seizures because the probability of finding a significant brain abnormality is very low (<2%) compared with a probability of 26% in children who have partial epilepsy.

Functional neuroimaging (SPECT, PET, and fMRI) generally is not part of the routine epilepsy investigation but can be useful for presurgical evaluation. SPECT and PET aim to localize the epileptic focus better. SPECT measures cerebral blood flow by using radiotracers (eg,  $^{99m}\text{Tc}$ -HMPAO) and takes advantage of the observation that cerebral blood flow is increased in the epileptogenic focus during a seizure. The interictal SPECT image is “subtracted” from the ictal SPECT to highlight areas of increased cerebral blood flow. PET estimates cerebral metabolism by using molecules such as  $^{18}\text{F}$ -2-deoxyglucose (FDG). The FDG-PET specifically

measures cerebral glucose utilization, which is correlated with neuronal activity. Focal hypometabolism generally is associated with an epileptogenic zone. The fMRI records blood oxygen variation in different brain regions during the execution of specific tasks by the patient. This technique allows localization of cerebral functions such as language.

### Neuropsychological Evaluation

A large proportion of children afflicted with epilepsy suffer from variable learning difficulties. The neuropsychological evaluation is especially helpful for characterizing these specific learning deficits and for developing strategies for improving school performance. The neuropsychological evaluation also is performed in most cases as part of the epilepsy presurgical evaluation to determine the patient’s cognitive deficits and, if surgery is not performed, the potential long-term consequences of epilepsy. The Wada test (also called Amytal<sup>®</sup> test) often is required prior to surgery to localize the brain hemisphere responsible for language and memory. This test consists



Figure 4. EEG tracing showing a right centroparietal spike (spikes observed in P4-O2, C4-P4, and F4-C4 leads) in a 12-year-old girl who has partial epilepsy.

of language and memory testing after one brain hemisphere is “anesthetized” following left or right internal carotid injection of sodium amobarbital.

## Treatment

### General Principles

Appropriate care of a child who has epilepsy is crucial because this condition carries significant emotional and social burdens. The first step is to educate the child and the parents about epilepsy. Demystification of this condition relieves a significant amount of anxiety. The patient should be informed about potential precipitating factors: sleep deprivation, hyperventilation, alcohol abuse, recreational drugs, and photic light stimulation. The child and the family should be instructed regarding seizure first aid. (For an example of a seizure first aid plan, see: [http://www.massgeneral.org/childhoodepilepsy/pdf/seizure\\_first\\_aid.pdf](http://www.massgeneral.org/childhoodepilepsy/pdf/seizure_first_aid.pdf).) Children who have epilepsy usually can participate in sports, but basic safety precautions must be taken to prevent serious injuries (eg, no swimming or bathing alone). Physicians should familiarize themselves with state regulations concerning

driving restrictions for patients who have a seizure history.

The second step involves discussing all strategies available to treat the seizures, which include antiepileptic drugs (AEDs), special diets, surgery, and vagus nerve stimulation. The decision to start an AED requires careful evaluation of the probability of seizure recurrence against the potential risks attributed to the medication. Most neurologists do not recommend AED treatment after a first seizure because only about 30% of patients have a second seizure. After two seizures, the risk of having a third one increases to about 75% without treatment. Thus, AED treatment generally is initiated after two seizures. Seizure control is achieved in most patients, but seizures become refractory to medication in about one third of patients.

**ANTIEPILEPTIC DRUGS.** Treatment is started with one AED, with the dose gradually increased until seizures are controlled with minimal toxicity. If the first drug fails to control seizures, the AED should be replaced by another. We usually recommend introducing the second drug



Figure 5. EEG tracing showing a generalized 3-Hz spike and wave discharge lasting 6 seconds in a 7-year-old girl who has generalized absence epilepsy.

and, if the child tolerates this new medication, weaning the patient from the first drug after a few weeks. If the second drug also is ineffective, a third medication can be tried alone or added in combination. The choice of AED depends primarily on the drug's efficacy against a specific seizure type, but the adverse effect profile, presence of other diseases, ease of use, and cost also must be considered.

Classically, valproic acid was considered the first choice for treating generalized epilepsy; carbamazepine was used for partial epilepsy. This scheme gradually is being modified as more experience is acquired with the newer AEDs, which appear to be as effective, safer, and better tolerated than the traditional medications (Table 1). Table 2 shows a list of available AEDs and their associated primary adverse effects. Classification of the patient's seizure type is crucial in choosing the appropriate AED. Some AEDs can worsen epilepsy if used to treat certain seizure types. For example, carbamazepine is known to aggravate generalized epilepsy in some patients.

Prior to AED treatment, blood should be drawn for a

complete blood count and for liver enzyme and kidney function tests. Baseline complete blood count, liver enzyme and kidney function tests, and regular blood AED concentrations usually are measured for the "traditional" AEDs (phenobarbital, phenytoin, valproic acid, carbamazepine). Blood AED concentrations are useful in estimating the potential for increasing AED dosage in patients whose seizures are uncontrolled, to check compliance, to determine dose-related toxicity, and to detect AED interactions in patients taking multiple AEDs (polytherapy).

When AEDs are used in combination, pharmacologic interactions can be problematic. Carbamazepine, phenytoin, and phenobarbital are well-known cytochrome P450 inducers and can increase the metabolism of other AEDs and of other medications (eg, oral contraceptives, steroids, warfarin). Valproic acid increases the plasma concentrations of phenobarbital, lamotrigine, and carbamazepine 10, 11-epoxide (toxic metabolite), but does not affect the efficacy of oral contraceptives.

Because chronic AED treatment generates potential morbidity, the benefits of discontinuing treatment must



Figure 6. EEG showing hypsarrhythmia in a 9-month-old girl who has infantile spasms.

be balanced against the risks of seizures recurring. Known risk factors for seizure recurrence after AED discontinuation are abnormal findings on neurologic examination, seizure onset before age 2 years, EEG abnormalities, and specific epilepsy types (eg, juvenile myoclonic epilepsy). Neurologists generally wait for a period of 1 to 2 seizure-free years before weaning a child off an AED.

**DIETS.** The ketogenic diet has been used for more than 80 years to treat children who have intractable epilepsy. For unknown reasons, this high-fat and low-carbohydrate diet sometimes provides dramatic improvement in seizure control and level of awareness. This diet requires extensive parent training and child supervision. The potential adverse effects are renal stones, growth inhibition, hyperlipidemia, vitamin deficiencies, and constipation. A new diet (low-glycemic index diet) is being developed and has the advantage of being less restrictive and more palatable than the ketogenic diet.

**SURGERY.** Epilepsy surgery is considered for patients who have seizures that seriously impair their quality of

life and who have a localized seizure focus that possibly could be resected without producing unacceptable sequelae. Most surgical techniques aim to remove the brain area responsible for the initiation of the seizure discharges. Such surgeries should be performed in specialized epilepsy centers. Extratemporal resections are undertaken more commonly in children than in adults because seizure foci in children are more likely to be due to focal dysgenesis. Hemispherectomy is indicated for conditions in which the entire hemisphere generates the epileptic activity (eg, hemimegalencephaly, Sturge-Weber syndrome, Rasmussen encephalitis). Corpus callosotomy is a palliative procedure used to prevent the propagation of epileptic activity from one hemisphere to the other. Corpus callosotomy is performed primarily in patients who have atonic seizures without any resectable lesion.

**VAGUS NERVE STIMULATOR.** The vagus nerve stimulator (VNS) is a pacemakerlike device that transmits electrical impulses to the left vagus nerve. A lead is attached to the vagus nerve and is connected to a stimulator inserted subcutaneously on the chest wall. The

**Table 1. Specific Use of Antiepileptic Drugs in Relation to the Epilepsy Types**

Absence	Primary Generalized		Partial Onset		
	Myoclonic, Atonic, Tonic	Tonic-Clonic	Simple Partial	Complex Partial	Secondary Generalized Tonic-Clonic
Ethosuximide	Benzodiazepines	Carbamazepine, Phenytoin, Phenobarbital, Primidone, Gabapentin, Tiagabine, Oxcarbazepine, Pregabalin			
	Valproate, Felbamate, Lamotrigine, Topiramate, Levetiracetam, Zonisamide				

current indication for VNS is as adjunctive treatment of intractable partial seizures. The mechanism of action is unknown, but presumably the stimulation modifies the brain's electrical activity. The device usually is well tolerated, but possible adverse effects include hoarseness, coughing, throat paresthesias, and dyspnea as well as the potential complications of the surgery itself.

**PSEUDOSEIZURES.** Management of nonepileptic events, or pseudo-seizures, often poses a special challenge for clinicians, especially when a patient who has epilepsy also has pseudo-seizures. Patient cooperation is crucial. After the diagnosis is made, an appropriate strategy is to explain that stress or emotions can cause seizurelike events unconsciously. It is important for the clinician to acknowledge the patient's distress. The patient also should be reassured that these events are not harmful to the

brain. The help of a mental health professional often is needed to work on potential stressors and emotional issues.

### Specific Disorders

**BENIGN PARTIAL EPILEPSY WITH CENTROTEMPORAL SPIKES.** Until recently, most neurologists believed that the seizures associated with this condition (also known as benign rolandic epilepsy) did not require treatment with AEDs, but this trend has changed, given the increasing literature on cognitive deficits associated with rolandic epilepsy. It now is recommended to start AEDs after two seizures. Almost all children enter long-term remission by mid-adolescence.

**TEMPORAL LOBE EPILEPSY.** Temporal lobe seizures often are refractory to AEDs. Temporal lobectomy is

**Table 2. Primary Adverse Effects Associated with Antiepileptic Drugs (AEDs)**

AED (abbreviations)	Primary Adverse Effects
Carbamazepine (CBZ)	Hepatic or blood dyscrasia, ataxia, diplopia, rash
Clobazam* (CLB)	Somnolence, ataxia, hyperactivity
Clonazepam (CLN)	Somnolence, hyperactivity
Ethosuximide (ESM)	Somnolence, blood dyscrasia
Felbamate (FBM)	Severe aplastic anemia, severe hepatic toxicity, weight loss
Gabapentin (GBP)	Ataxia, fatigue
Lamotrigine (LTG)	Rash, ataxia, insomnia
Levetiracetam (LEV)	Somnolence, ataxia, behavioral changes
Oxcarbazepine (OXC)	Hepatic or blood dyscrasia, ataxia, diplopia
Phenobarbital (PB)	Somnolence, cognitive impairment
Phenytoin (PHT)	Ataxia, nystagmus, somnolence, gingival hyperplasia, hirsutism, rash
Pregabalin (PGB)	Ataxia, fatigue
Tiagabine (TGB)	Fatigue
Topiramate (TPM)	Cognitive impairment, weight loss, kidney stones
Valproic acid (VPA)	Severe hepatic toxicity, weight gain, osteopenia
Vigabatrin* (VGB)	Dizziness, retinal degeneration
Zonisamide (ZNS)	Cognitive impairment, somnolence, weight loss, dizziness, kidney stones

\*Not available in United States.

effective in approximately 80% of cases if mesial temporal sclerosis is observed on MRI.

**FRONTAL LOBE EPILEPSY.** Surgery is less beneficial for this condition than for temporal lobe epilepsy because the seizure focus is harder to localize and lateralize and because larger brain areas often need to be resected. With improving MRI resolution, better outcomes are expected after epilepsy surgery for frontal lobe epilepsy.

**CHILDHOOD ABSENCE EPILEPSY.** A good treatment response is expected with valproic acid, ethosuximide, or lamotrigine. Seizures usually remit by adolescence or early adulthood.

**JUVENILE MYOCLONIC EPILEPSY (JANZ SYNDROME).** More than 80% of patients who have this condition are well controlled on broad-spectrum AEDs, but the seizures frequently relapse when the medication is discontinued, and treatment often is required into adulthood.

**INFANTILE SPASMS.** Medication controls spasms completely in approximately 75% of cases. Early control of spasms is associated with a better cognitive outcome. Commonly used first-line drugs are vigabatrin (not available in the United States) and adrenocorticotropic hormone; benzodiazepines, valproic acid, and topiramate are considered second-line therapy. The ketogenic diet and other broad-spectrum AEDs also may be effective. Carbamazepine sometimes precipitates the occurrence of spasms.

**LENNOX-GASTAUT SYNDROME.** Seizure control in Lennox-Gastaut syndrome is very difficult, and polytherapy is common. Valproic acid, lamotrigine, topiramate, and clonazepam are used commonly, with variable effects on the different seizure types. Felbamate can be effective but may be associated with significant morbidity. The ketogenic diet and VNS also may improve seizure control. Corpus callosotomy can reduce or abolish drop attacks if there is no underlying major diffuse brain malformation, but that procedure rarely influences the other seizure types seen in Lennox-Gastaut syndrome.

**FEBRILE SEIZURES.** Administration of an antipyretic (acetaminophen or ibuprofen) during febrile episodes is recommended for children who experience recurrent febrile seizures. Preventive anticonvulsant medication should be reserved for children who have frequent febrile seizures. Intermittent prevention strategy involves administering rectal diazepam (0.5 mg/kg) when the sei-

zure occurs or oral diazepam during the febrile episode (1 mg/kg per day divided in three doses). If the intermittent strategy is insufficient, continuous treatment with anticonvulsant medications can be started.

### Status Epilepticus

The initial management of a child in status epilepticus is to secure the airway. The child should be placed on his or her side to prevent aspiration, making sure that the upper respiratory airway is free and oxygen is provided by mask. Blood pressure and electrocardiographic monitoring should be instituted. While gathering information from the parents and examining the patient, blood should be drawn for a complete blood count, electrolytes, blood glucose, calcium, and magnesium and toxicologic screen. An intravenous (IV) line should be placed. If the patient is known to have epilepsy and taking medication, concentrations of AEDs should be determined. Any potentially epileptogenic metabolic imbalance should be corrected quickly.

If the seizure is not caused by metabolic derangement, the general consensus is to start treatment with a benzodiazepine. IV lorazepam at a dose of 0.1 mg/kg (0.15 mg/kg for patients already receiving a benzodiazepine) up to a maximum of 4 mg is generally the first choice. Diazepam at a dose of 0.3 mg/kg (0.5 mg/kg for patients already receiving a benzodiazepine) also is a good option and can be administered intravenously, intrarectally, or endotracheally. Lorazepam or diazepam can be repeated at the same dose if the seizure does not stop after 5 minutes.

The second step is to use IV phenytoin or phenobarbital. Phenytoin (or fosphenytoin) is given at a dose of 20 mg/kg intravenously (or 20 phenytoin equivalents/kg) up to a maximum of 1,250 mg. Phenytoin (or fosphenytoin) usually is ineffective for febrile status epilepticus. Phenobarbital is administered at a dose of 10 to 20 mg/kg, up to a maximum of 300 mg. If the seizure remains uncontrolled, the third step is to induce a "barbiturate coma." At this stage, intubation is mandatory, and an anesthesiologist should be involved. Status epilepticus treatment protocols vary at different institutions. Some physicians may use midazolam, valproic acid, or other AEDs.

### Conclusion

Many investigational tools are available to refine the clinical evaluation of seizures in children. The additional information gained from these studies helps to determine appropriate prognosis and treatment. Educating the child and family about seizure disorders is another key element in effective management.

**ACKNOWLEDGMENTS.** We are very thankful to Dr Ron Thibert for his help in the preparation of this article.

### Suggested Reading

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## PIR Quiz

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

1. A worried mother brings in her 16-year-old daughter for concerns over seizures at school. Her teacher reported that within 1 hour, the girl had three episodes of groaning and shaking all over with her eyes shut tight and her head moving from side to side. Each episode lasted approximately 3 minutes. There was no respiratory difficulty or urinary or fecal incontinence, and between episodes, the girl was awake and quiet but appropriately responsive. Additional history reveals no prior seizures and a recent move to the new school. Her physical examination findings are normal. Of the following, the test that is *most* likely to reveal the diagnosis is:
  - A. Antinuclear antibody measurement.
  - B. Computed tomography scan of the brain.
  - C. Lumbar puncture.
  - D. Urine toxicology screen.
  - E. Video electroencephalography.
2. A 17-year-old girl who has had seizures for the past 5 years presents to your office. Her seizures have been well controlled (none in 2 years) on her current antiepileptic medication, and she asks you if it can be discontinued. Physical examination findings are normal. Of the following, the factor that is *most* likely to increase her risk of seizure recurrence after discontinuing her medication is:
  - A. Diagnosis of benign rolandic epilepsy.
  - B. Diagnosis of juvenile myoclonic epilepsy.
  - C. Family history of epilepsy.
  - D. History of developmental delay as a young child.
  - E. History of status epilepticus with initial seizure.
3. Of the following antiepileptic medications, which one is *most* likely to cause nephrolithiasis?
  - A. Ethosuximide.
  - B. Lamotrigine.
  - C. Phenobarbital.
  - D. Topiramate.
  - E. Valproic acid.
4. Of the following, which seizure type is matched correctly with the appropriate antiepileptic medication?
  - A. Absence epilepsy — Gabapentin.
  - B. Atonic epilepsy — Phenytoin.
  - C. Complex partial epilepsy — Carbamazepine.
  - D. Simple partial epilepsy — Midazolam.
  - E. Tonic-clonic epilepsy — Ethosuximide.

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