Seizures in Children

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Seizures are the most common pediatric neurologic disorder, with 4\% to 10\% of children suffering at least one seizure in the first 16 years of life [1]. The incidence is highest in children younger than 3 years of age, with a decreasing frequency in older children [2]. Epidemiologic studies reveal that approximately 150,000 children will sustain a first-time, unprovoked seizure each year, and of those, 30,000 will develop epilepsy [1].

A seizure is defined as a transient, involuntary alteration of consciousness, behavior, motor activity, sensation, or autonomic function caused by an excessive rate and hypersynchrony of discharges from a group of cerebral neurons. A postictal period of decreased responsiveness usually follows most seizures, in which the duration of the postictal period is proportional to the duration of seizure activity. Epilepsy describes a condition of susceptibility to recurrent seizures. The classic definition of status epilepticus refers to continuous or recurrent seizure activity lasting longer than 30 minutes without recovery of consciousness.

During a seizure, cerebral blood flow, oxygen and glucose consumption, and carbon dioxide and lactic acid production all increase. Early systemic changes include tachycardia, hypertension, hyperglycemia, and hypoxemia. Brief seizures rarely produce lasting effects on the brain. Prolonged seizures, however, can lead to lactic acidosis, rhabdomyolysis, hyperkalemia, hyperthermia, and hypoglycemia, all of which may be associated with permanent neurologic damage. Airway management and termination of the seizure are the initial priorities in patients who are actively seizing.
Classification of seizures

Seizures are classified as generalized or partial. Generalized seizures are associated with the involvement of both cerebral hemispheres. They may be convulsive, with prominent motor activity, or nonconvulsive. Motor involvement, when present, is usually bilateral. Generalized seizures may also involve an altered level of consciousness. Types of generalized seizures include tonic-clonic (grand mal), tonic, clonic, myoclonic, atonic-akinetic (drop attacks) or absence (petit mal) [3,4]. Generalized tonic-clonic seizures are the most common type of childhood seizure. Most tonic-clonic seizures have a sudden onset, although a small percentage of children may experience a motor or sensory aura. During the initial tonic phase, the child becomes pale, with dilation of the pupils, deviation of the eyes, and sustained contraction of muscles with progressive rigidity. Bladder or bowel incontinence is common. Clonic movements, involving rhythmic jerking and flexor spasms of the extremities, then occur. Mental status is usually impaired during the seizure and for a variable time after the seizure has ceased. Myoclonic seizures are characterized by an abrupt head drop with arm flexion and may occur up to several hundred times daily. Atonic seizures are characterized by a sudden loss of both muscle tone and consciousness. Simple (typical) absence seizures are uncommon before the age of 5 years and are characterized by a sudden cessation of motor activity, a brief loss of awareness, and an accompanying blank stare. Flickering of the eyelids may be seen. The episodes last less than 30 seconds and are not associated with a postictal period. Complex (atypical) absence seizures are usually associated with myoclonic activity in the face or extremities and an altered level of consciousness [2,3].

Partial seizures may be simple, with no impairment of consciousness, or complex, with altered mental status. Both simple and complex partial seizures may progress to secondarily generalized seizures in up to 30% of children. Simple partial seizures are associated usually with abnormal motor activity developing in a fixed pattern on the hands or face. Although simple partial seizures are associated most commonly with motor abnormalities, sensory, autonomic, and psychic manifestations also may be seen. Complex partial seizures (temporal lobe seizures) are characterized by changes in perception and sensation, with associated alterations in consciousness [3]. Seizures tend to affect the eyes (a dazed look), the mouth (lip smacking and drooling), and the abdomen (nausea and vomiting) [1]. There are other specific seizure syndromes that also occur in children.

Lennox-Gastaut syndrome has an onset between 3 and 5 years of age and is characterized by intractable mixed seizures with a combination of tonic, myoclonic, atonic, and absence seizures. Most of these children also have accompanying mental retardation and severe behavioral problems. The EEG shows an irregular, slow, high-voltage spike pattern [2,3]. Although many drugs have been used to treat this condition, management is still very difficult. Valproic acid is the drug used most commonly; however, felbamate, topiramate, lamotrigine, and zonisamide have also been used as adjunctive therapies [5,6]. The ketogenic diet has also been used with some success in these children [7].
Children between 3 and 13 years of age who suffer from benign rolandic epilepsy experience nighttime seizures during sleep. This seizure disorder is genetically inherited as an autosomal dominant trait. The initial phase of the seizure involves clonic activity of the face, including grimacing and vocalizations, which often wake the child from sleep. An electroencephalogram (EEG) is important in the evaluation of this condition because a characteristic perisylvian spiking pattern can be seen. Unless these seizures are frequent, no therapy is needed because patients usually will outgrow these episodes by early adulthood. Carbamazepine has been used with success in the treatment of frequent rolandic seizures [1–3,6].

Juvenile myoclonic epilepsy of Janz is inherited as an autosomal dominant trait that manifests in early adolescence (onset 12–18 years of age). Patients experience myoclonic jerks typically on awakening but may also have tonic-clonic (80%) or absence (25%) seizures. Typical provoking factors include stress, alcohol, hormonal changes, or lack of sleep. The EEG is helpful in the diagnosis because a pattern of fast spike-and-wave discharges can be seen. Valproic acid is the drug of choice, with lamotrigine, topiramate, felbamate, and zonisamide as alternate options [1–3,6].

Children with infantile spasms (West’s syndrome) present typically between 4 and 18 months of age, with males affected more commonly than females. Up to 95% of affected children are mentally retarded, and there is a 20% mortality rate. Patients experience sudden jerking contractions of the extremities, head, and trunk. The jerking is spasmodic and often occurs in clusters. Episodes rarely occur during sleep. Up to 25% of patients have tuberous sclerosis. The EEG shows the classic pattern of hypsarrhythmia (random high-voltage slow waves with multifocal spikes) [2,3]. Treatment with adrenocorticotropic hormone (ACTH) and prednisone has been used with some success [6,8]. Valproic acid, topiramate, lamotrigine, vigabatrin, and zonisamide have also shown some effectiveness [5,6,9,10].

**Differential diagnosis**

A seizure represents a clinical symptom of an underlying pathologic process with many possible causes (Box 1). When a child presents with a seizure, every effort should be made to determine the cause. It is imperative to differentiate between a seizure and other nonepileptic conditions that may mimic seizure activity (Box 2). A detailed description of the event from a witness is the most important factor in an accurate diagnosis. If a historical detail does not seem typical for a seizure, an alternative diagnosis should be considered.

Nonepileptic events that involve altered levels of consciousness are common in childhood. Unlike seizures, there is no postictal phase following these episodes. Breath-holding spells affect approximately 5% of children between the ages of 6 months and 5 years. A cyanotic spell begins with a period of vigorous crying followed by breath-holding, cyanosis, rigidity, limpness, and often,
Box 1. Causes of seizures

**Infectious**
- Brain abscess
- Encephalitis
- Febrile seizure
- Meningitis
- Neurocysticercosis

**Neurologic or developmental**
- Birth injury
- Congenital anomalies
- Degenerative cerebral disease
- Hypoxic-ischemic encephalopathy
- Neurocutaneous syndromes
- Ventriculoperitoneal shunt malfunction

**Metabolic**
- Hypercarbia
- Hypocalcemia
- Hypoglycemia
- Hypomagnesemia
- Hypoxia
- Inborn errors of metabolism
- Pyridoxine deficiency

**Traumatic or vascular**
- Cerebral contusion
- Cerebrovascular accident
- Child abuse
- Head trauma
- Intracranial hemorrhage

**Toxicologic**
- Alcohol, amphetamines, antihistamines, anticholinergics
- Cocaine, carbon monoxide
- Isoniazid
- Lead, lithium, lindane
- Oral hypoglycemics, organophosphates
- Phencyclidine, phenothiazines
- Salicylates, sympathomimetics
- Tricyclic antidepressants, theophylline, topical anesthetics
- Withdrawals (alcohol, anticonvulsants)

**Idiopathic or epilepsy**

**Obstetric (eclampsia)**

**Oncologic**
Box 2. Pediatric conditions often mistaken for seizures

**Disorders with altered consciousness**
- Apnea and syncope
- Breath-holding spells
- Cardiac dysrhythmias
- Migraine

**Paroxysmal movement disorders**
- Acute dystonia
- Benign myoclonus
- Pseudoseizures
- Shuddering attacks
- Spasmus mutans
- Tics

**Sleep disorders**
- Narcolepsy
- Night terrors
- Sleepwalking

**Psychologic disorders**
- Attention deficit hyperactivity disorder
- Hyperventilation
- Hysteria
- Panic attacks

**Gastroesophageal reflux (Sandifer’s syndrome)**

Twitching of the extremities. A pallid spell begins with an inciting painful stimulus, followed by pallor and a brief loss of consciousness. In both types of breath-holding spells, recovery to baseline is rapid and complete. Syncope is a brief, sudden loss of consciousness usually preceded by a feeling of light-headedness. On recovery, the child may be pale and diaphoretic but responsive. Patients with atypical migraines experience altered consciousness that is often associated with blurred vision, dizziness, and a loss of postural tone [2,3,11].

Paroxysmal movement disorders involve abnormal motor activity and may mimic seizures; however, altered consciousness is rare with these events. Tics are brief, repetitive movements that may be induced by stress and are usually suppressible. Shuddering attacks are whole-body tremors lasting a few seconds with a rapid return to normal activity. Acute dystonia is characterized by an involuntary sustained contraction of the neck and trunk muscles, with abnormal posture and facial grimacing. Dystonic reactions in children are seen most often as a side effect of certain medications. Pseudoseizures may present with a variety of paroxysmal movements, may be difficult to distinguish from a true seizure, and are often seen in children who have a relative with epilepsy or in patients who have a true seizure disorder. Features suggestive of a pseudoseizure
include a lack of coordination of movements, moaning or talking during the episode, the absence of incontinence or bodily injury, and suggestibility. Benign myoclonus is marked by self-limited, sudden jerking movements of the extremities, usually on falling asleep. Spasms nutans occurs in children 4 to 12 months of age and causes head tilt, nodding, and nystagmus. Infants with Sandifer’s syndrome (gastroesophageal reflux) present with crying, vomiting, and writhing, arching movements of the neck and back [2,3,11,12].

Some nonepileptic paroxysmal events are associated with sleep and can be differentiated from seizures by their characteristic alterations in behavior. Night terrors occur in the preschool-aged child, with a sudden awakening from sleep, followed by crying, screaming, and inconsolability. The child then returns to sleep and has no recollection of the event. Sleepwalking (somnambulism) is seen in school-aged children who awaken from sleep with a glassy stare and walk around aimlessly for several seconds. The child then falls back asleep easily on returning to bed. Narcolepsy often presents in adolescence with an abrupt change of alertness and uncontrollable daytime sleepiness. Oftentimes, narcolepsy is associated with cataplexy, the sudden loss of muscle tone with preservation of consciousness [2,3,11].

History and physical examination

Obtaining a detailed history is critical in the evaluation of a seizure because of the many possible causes of a seizure as well as the numerous conditions that can simulate a seizure. The history should focus on both the events immediately before the onset of the episode as well as a thorough description of the actual seizure. The information to elicit includes the duration, movements, eye findings, cyanosis, loss of consciousness, the presence of an aura, incontinence, length of the postictal period, and any post-seizure focal neurologic abnormalities. Further information to obtain includes potential precipitating factors such as trauma, ingestion, recent immunizations, fever, or other systemic signs of illness. Home therapies for any recent illnesses should also be determined. If it is known that the child has a seizure disorder, then it is important to ascertain whether the recent seizure was different from previous seizures, the typical seizure frequency for the patient, any medications the patient is taking, and whether the patient has been compliant with the medication regimen or there have been any recent medication changes. Additional history to elicit includes other significant medical problems (neurologic disease, presence of a ventriculoperitoneal [VP] shunt, or developmental delay), recent travel history, and a family history of seizures.

A thorough physical and neurologic examination should be performed. Vital signs, including temperature, heart rate, and blood pressure, should be obtained. Fever is the most common cause of seizures in children (as discussed later). The head should be examined for microcephaly, dysmorphic features, signs of trauma, and the presence of a VP shunt. In infants, a measurement of the head circumference may be helpful. A bulging fontanelle indicates increased intracranial
pressure. The eyes should be examined for papilledema and retinal hemorrhages. Evaluate the neck for signs of meningeal irritation. The presence of hepatospleno-megaly may indicate a metabolic or glycogen storage disease. Assess the skin for lesions such as café au lait spots (neurofibromatosis), adenoma sebaceum or ash leaf spots (tuberous sclerosis), and port wine stains (Sturge-Weber syndrome). Unexplained bruising should raise the suspicion of a bleeding disorder or child abuse [3].

Diagnostic approach

Laboratory testing

Laboratory testing for a child who has an afebrile seizure should be guided by the history and physical examination. A rapid bedside glucose test should be performed. A drug level should be obtained in patients who are taking anticonvulsant medications [4]. The determination of serum electrolytes, calcium, magnesium, ammonia, white blood cell count, and toxicology screens may not be necessary in a child who is alert and has returned to a baseline level of function and should be based on clinical suspicion [13]. In patients who have no identifiable risk factors, an accurate and thorough history and physical examination have been shown to yield more diagnostic information than a laboratory evaluation [14]. However, newborns and infants less than 6 months of age have been found to be at a greater risk for electrolyte abnormalities because of underlying metabolic abnormalities, specifically hyponatremia resulting from the increased free water intake from formula overdilution [15]. Patients who have abnormal electrolyte values are more likely to have been actively seizing on presentation, have hypothermia (temperature less than 36.5°C), or be younger than 1 month of age [16]. A temperature lower than 36.5°C has been shown to be the best predictor of hyponatremia-induced seizures in infants younger than 6 months of age [17]. Based on the results of these reports, it is reasonable to obtain laboratory studies on pediatric patients who have prolonged seizures, are younger than 6 months of age, have a history of diabetes, metabolic disorder, dehydration, or excess free water intake, and patients who have an altered level of consciousness.

Routine lumbar puncture is not indicated in patients who are alert and oriented after a first afebrile seizure. A lumbar puncture should be considered after neonatal seizures occur and should be performed in patients who have an altered mental status, signs of meningeal irritation, or a prolonged postictal period [13].

Neuroimaging

Emergent neuroimaging typically is not necessary in well-appearing children after a first, unprovoked nonfebrile seizure [13]. Radiologic imaging of the seizure patient in an emergency setting usually consists of a computed CT scan of the brain. A CT scan is indicated in the acute evaluation of patients who have
a focal seizure or persistent seizure activity, a focal neurologic deficit, a VP shunt, a neurocutaneous disorder, signs of elevated intracranial pressure, and a history of trauma or travel to an area endemic for cysticercosis. Patients who have immuno-compromising diseases (malignancy or HIV), hypercoagulable states (sickle cell disease), or bleeding disorders are also candidates for emergent imaging [18,19]. A MRI study is more sensitive than a cranial CT scan for the detection of certain tumors and vascular malformations. However, MRI is not readily available on an emergent basis [3,4]. Emergent imaging should be performed only in patients who have high-risk criteria. Low-risk patients can be discharged for follow-up without undergoing immediate imaging [13].

Electroencephalography

An EEG is rarely needed in the acute setting, except for patients who have refractory seizures or in patients in whom the diagnosis of nonconvulsive status epilepticus is being considered. Well-appearing children who have experienced a first-time afebrile seizure should be referred for outpatient EEG testing [3,4]. An ictal EEG taken during a seizure event is most useful, but because this is not always possible, a complete EEG recording should include both sleep and wake cycles as well as periods of patient stimulation. It is important to note, however, that a normal EEG does not rule out epilepsy or other underlying neurologic disorders [20].

Management

Acute stabilization

Status epilepticus should be considered in any patient who presents to an acute care setting with active seizure activity. An algorithm for the management of status epilepticus is presented in Fig. 1. The initial management should focus on the stabilization of the airway, breathing, and circulation and stopping the seizure. The patient should be positioned to allow for an open airway, and if necessary, an oral or nasal airway should be inserted. Oxygen should be administered and further equipment for assisted ventilation should be at the bedside. Intravenous (IV) access should be established promptly. The actively convulsing patient should also be protected from self-inflicted trauma. A rapid glucose level determination should be performed at the bedside, and a glucose infusion should be initiated for documented hypoglycemia. Dextrose should not be given empirically to children on ketogenic diets because this will break the ketogenic state and may result in increased seizure activity. Naloxone should be administered in cases of suspected drug exposures. The administration of pyridoxine should be considered in neonates and those with possible isoniazid ingestion [21–24].

Most patients who present with active convulsions will require pharmacologic treatment to end the seizure. Benzodiazepines are the initial drugs of choice for
Establish ABCs: Maintain airway, give oxygen, support ventilation, establish IV access

↓

Consider IV glucose, naloxone, or pyridoxine based on clinical scenario

↓

First dose of benzodiazepine:
- Lorazepam 0.05 – 0.1 mg/kg IV
- Diazepam 0.5 mg/kg PR
- Midazolam 0.2 mg/kg IM

$Seizure \text{ continues at } 5-15 \text{ min} \quad \downarrow \quad \text{May repeat benzodiazepine 1-2x}$

Phenytoin or fosphenytoin 15-20 mg/kg IV

$Seizure \text{ continues at } 15-30 \text{ min} \quad \downarrow$

Phenobarbital 20 mg/kg IV

$Seizure \text{ continues > } 30 \text{ min} \quad \downarrow \quad \text{Re-assess airway/consider intubation}$

Continuous infusion of pentobarbital, midazolam, propofol

$Seizure \text{ continues > } 60 \text{ min} \quad \downarrow \quad \text{Intubate now}$

General anesthesia

Fig. 1. An algorithm for the management of status epilepticus. ABC, airway, breathing, circulation; PR, administered rectally.

The acute management of seizures [21,24]. Lorazepam is the preferred agent because of its rapid onset (2–5 minutes) and long half-life (12–24 hours). It can be given in the IV or intramuscular (IM) form at a dose of 0.05 to 0.1 mg/kg (maximum 4 mg/dose). The dose may be repeated after 5 to 15 minutes, but the drug’s effectiveness decreases with subsequent doses [4,24]. Diazepam has a rapid onset but a much shorter half-life (less than 30 minutes) than lorazepam. If diazepam is given for seizure termination, a long-term agent should be used in addition to prevent seizure recurrence. Diazepam can be given in a dose of 0.2 to 0.4 mg/kg IV or intraosseous (IO) (maximum 10 mg/dose). If IV access is not readily available, diazepam can also be given rectally, administering the IV formulation at a dose of 0.5 mg/kg [24–26]. Another agent to consider is midazolam, which can be administered by many routes, including IV, IM, rectal, intranasal, and buccal [24,26–28]. The major side effects of the benzodiazepines are respiratory depression and sedation, especially with repeated doses or in combination with a barbiturate.

Phenytoin or fosphenytoin is administered if a seizure continues despite the use of benzodiazepine. Phenytoin can only be instilled by IV at a loading dose of 10 to 20 mg/kg, with each 1 mg/kg of drug given, raising the serum concentration
Phenytoin has a peak effect at 10 to 20 minutes after completion of the infusion and a duration of action of 12 to 24 hours. Phenytoin must be administered slowly (0.5–1.0 mg/kg/min to a maximum of 50 mg/kg/min) and under cardiac monitoring because of the risk of hypotension and cardiac dysrhythmias with rapid infusion. Furthermore, it cannot be mixed in a dextrose-

### Table 1
Common anticonvulsant agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Side effects</th>
<th>Maintenance (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Generalized tonic-clonic, partial, benign rolandic seizures</td>
<td>Rash, hepatitis, diplopia, aplastic anemia, leukopenia</td>
<td>10–40 mg/kg/day</td>
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<tr>
<td>(Tegretol)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clonazepam</td>
<td>Myoclonic, akinetic, partial seizures, infantile spasms, Lennox-Gastaut</td>
<td>Fatigue, behavioral issues, salivation</td>
<td>0.05–0.30</td>
</tr>
<tr>
<td>(Klonopin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Absence</td>
<td>GI upset, weight gain, lethargy, SLE, rash</td>
<td>20–40</td>
</tr>
<tr>
<td>(Zarontin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>Re refractory severe epilepsy</td>
<td>Aplastic anemia, hepatotoxicity</td>
<td>15–45</td>
</tr>
<tr>
<td>(Felbatol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Partial and secondarily generalized seizures</td>
<td>Fatigue, dizziness diarrhea, ataxia</td>
<td>20–70</td>
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<tr>
<td>(Neurontin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Complex partial, atonic, myoclonic, absence, tonic-clonic, Lennox-Gastaut, infantile spasms</td>
<td>Headache, nausea, rash, diplopia, Stevens-Johnson synd, GI upset</td>
<td>5–15</td>
</tr>
<tr>
<td>(Lamictal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Adjunctive therapy for refractory partial seizures</td>
<td>Headache, anorexia, fatigue, infection</td>
<td>10–60</td>
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<tr>
<td>(Keppra)</td>
<td></td>
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<tr>
<td>Oxcarbazepine</td>
<td>Adjunctive therapy for partial seizures</td>
<td>Fatigue, low sodium, nausea, ataxia, rash</td>
<td>10–45</td>
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<tr>
<td>(Trileptal)</td>
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<tr>
<td>Phenytoin</td>
<td>Generalized tonic-clonic, partial, atonic, myoclonic, neonatal</td>
<td>Gum hyperplasia, hirsutism, ataxia, Stevens-Johnson syndrome, lymphoma</td>
<td>4–8</td>
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<tr>
<td>(Dilantin)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Primidone</td>
<td>Generalized tonic-clonic, partial</td>
<td>Rash, ataxia, behavioral issues, sedation, anemia</td>
<td>10–25</td>
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<tr>
<td>(Mysoline)</td>
<td></td>
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<td></td>
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<tr>
<td>Tiagabine</td>
<td>Adjunctive therapy for refractory complex partial (focal) seizures</td>
<td>Fatigue, headache tremor, dizziness, anorexia</td>
<td>0.10 mg/kg/d; avg. dose 6 mg/d</td>
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<tr>
<td>(Gabitril)</td>
<td></td>
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<tr>
<td>Topiramate</td>
<td>Refractory complex partial seizures, adjunctive therapy for temporal lobe epilepsy</td>
<td>Fatigue, nephrolithiasis, ataxia, headache, tremor, GI upset</td>
<td>1–9</td>
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<tr>
<td>(Topamax)</td>
<td></td>
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<td></td>
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<tr>
<td>Valproic acid</td>
<td>Generalized tonic-clonic, absence, myoclonic, partial, akinetic, infantile spasms</td>
<td>GI upset, liver involvement, tremor, alopecia, sedation, weight gain</td>
<td>10–60</td>
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<tr>
<td>(Depakote)</td>
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<tr>
<td>Vigabatrin</td>
<td>Infantile spasms, adjunctive therapy for refractory seizures</td>
<td>Weight gain, behavior changes, visual field constriction</td>
<td>30–150</td>
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<tr>
<td>(Sabril)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Zonisamide</td>
<td>Adjunctive therapy for partial seizures, atonic, infantile spasms</td>
<td>Fatigue, ataxia, anorexia, GI upset, headache, rash</td>
<td>2–8</td>
</tr>
<tr>
<td>(Zonegran)</td>
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</table>

*Abbreviation: SLE, systemic lupus erythematosus.*
containing solution because of precipitation problems. Local reactions such as thrombophlebitis are common following infusion, and tissue necrosis may be seen with accidental infiltration [4,21–24]. Phenytoin is a prodrug developed recently whose active metabolite is phenytoin. Its advantages include a more rapid administration (3 mg/kg/min to a maximum of 150 mg/min), fewer local and systemic side effects, the option of IM injection, and the ability to give the drug in a saline or dextrose-containing solution. The drug is dosed as phenytoin equivalents (PE) with a loading dose of 10 to 20 mg of PE/kg [4,24,29].

Phenobarbital is the next drug to be added if seizures persist. In neonates, however, phenobarbital is the initial drug of choice. It is given in a loading dose of 20 mg/kg, with an onset of action in 15 to 20 minutes and an anticonvulsant duration effect of between 24 and 120 hours. It causes significant sedation, hypotension, and respiratory depression, especially when used in conjunction with a benzodiazepine [4,21–24].

Continuous infusions of pentobarbital, midazolam, or propofol may be needed for refractory seizures. The patient should be ventilated mechanically and have continuous EEG monitoring. The medication should be titrated to maintain a flat-line or suppression pattern on the EEG. If seizures continue for more than 1 hour despite the above therapies, patients may require general anesthesia, neuromuscular blockade, and continuous EEG monitoring in an intensive care setting [3,21–23].

Long-term treatment

The decision to initiate treatment with an anticonvulsant medication is based on many factors. Considerations include the patient’s age, type of seizure, risk of recurrence, and other predisposing medical issues. Maintenance medications are usually not initiated for stable, well-appearing children after a single afebrile seizure. Although anticonvulsant agents may decrease the incidence of a second seizure, they do not reduce the long-term risk of developing epilepsy. Patients who experience recurrent seizures, however, should be started on an antiepileptic medication. The decision to initiate long-term anticonvulsant therapy should be made in conjunction with the patient’s primary care provider or a neurologist [13,20,30].

There are numerous agents available to prevent pediatric seizures (Table 1). Several guidelines have been suggested to aid in the choice of an anticonvulsant medication [3,10,31].

1. Choose an agent that is effective for the particular type of seizure. If several drugs are available, use the drug that is least toxic.
2. Initiate therapy with a single agent.
3. Start at the low end of the dosage range.
4. Continue the same drug for at least long enough to reach a steady state, usually five times the half-life of the drug.
5. Increase the dosage until seizure control is achieved or unacceptable side effects occur.

6. Consider adding another agent if the patient continues to have seizure activity. Aim for a goal of monotherapy by eventually eliminating the first drug.

Carbamazepine (Tegretol) is useful for treating generalized tonic-clonic, simple, and complex partial seizures. It is also the drug of choice for treating benign rolandic epilepsy [2]. Recommended maintenance doses range from 10 to 40 mg/kg divided into 2 or 3 daily doses. Doses should be started at 5 mg/kg and increased by 5 mg/kg every 3 to 4 days until an effective maintenance level is achieved. Therapeutic serum levels range from 4 to 12 µg/mL. Dose-related adverse effects include drowsiness, blurred vision, and lethargy. Other side effects include rash, leukopenia, aplastic anemia, and hepatic toxicity. Toxic carbamazepine levels may result from the concomitant use of macrolide antibiotics, cimetidine, isoniazid, and certain calcium channel blockers. Carbamazepine may also interfere with the effectiveness of oral contraceptives [30–32].

Phenytoin (Dilantin) is effective against generalized tonic-clonic and both types of partial seizures. The usual maintenance dose ranges from 4 to 8 mg/kg/d given once, twice, or three times daily. Therapeutic serum levels range from 10 to 20 µg/mL. Because of varying rates of absorption of the drug, small dosage changes can result in large changes in serum drug levels. Similarly, drug levels may also be affected if either the trade or generic form of the drug is substituted for the other. Nondose-dependent adverse effects include gingival hyperplasia, hirsutism, and acne. These cosmetic side effects may limit the drug’s long-term use, especially in girls. Other side effects include drug-induced rashes (Stevens-Johnson syndrome) and blood and liver toxicity. Dose-related toxic effects, such as nausea, vomiting, drowsiness, ataxia, and nystagmus, usually occur with levels outside the therapeutic range. Phenytoin can interfere with the effectiveness of other anticonvulsant agents, decreasing serum levels of carbamazepine, clonazepam, and primidone, and increasing the serum concentration of phenobarbital. The administration of cimetidine, estrogens, chlorpromazine, chloramphenicol, isoniazid, and anticoagulants may result in an increased phenytoin drug level [24,30–32].

Phenobarbital (Luminol) is useful for treating generalized tonic-clonic and partial seizures and is a first-line agent for treating neonatal seizures. The usual dose ranges from 2 to 6 mg/kg/d, given once or twice daily, with a therapeutic range of 10 to 40 µg/mL. Phenobarbital is fairly inexpensive and so is used commonly as a the initial drug. However, it does have several undesirable side effects in 30 to 50% of children who experience hyperactivity, mood alterations, cognitive dysfunction, and sleep problems. These common behavioral effects cause many clinicians to limit the use of this drug [24,30,32].

Primidone (Mysoline) is metabolized to phenobarbital, so the two drugs are useful for treating the same types of seizures, and both cause similar side effects. The usual dose is between 10 and 25 mg/kg/d, given in two to four divided doses.
Maintenance doses should be started at the low end of the dosage range because excessive sedation and ataxia are common at higher doses. The therapeutic range is between 5 and 12 µg/mL and is measured by monitoring the serum level of phenobarbital [30–32].

Valproate (Depakote) is quite effective for the treatment of absence and myoclonic seizures but can be used for generalized tonic-clonic and partial seizures as well. Valproic acid has also been used with success in the treatment of Lennox-Gastaut seizures, juvenile myoclonic epilepsy of Janz, and occasionally in the management of infantile spasms [2,5]. The typical maintenance dose ranges from 10 to 60 mg/kg/d, divided two to four times daily. Daily doses should be initiated at 10 mg/kg and increased by 10 mg/kg weekly until a therapeutic serum level of 50 to 100 µg/mL is established. Common side effects include gastrointestinal (GI) upset, weight gain, drowsiness, and alopecia. Tremors and thrombocytopenia are dose-related effects. Children less than 2 years of age are at an increased risk for liver and pancreatic toxicity. Valproate interferes with the metabolism of other anticonvulsant agents and may increase the drug levels of phenobarbital, phenytoin, carbamazepine, diazepam, clonazepam, and ethosuxamide [30–32].

Ethosuxamide (Zarontin) is most effective for the treatment of absence seizures. The maintenance dose ranges from 20 to 40 mg/kg/d, divided into two daily doses, with an optimal therapeutic serum level of 40 to 100 µg/mL. Common side effects include GI upset, weight gain, and headache, with the rare occurrence of erythema multiforme and a lupus-like syndrome [30,31].

Clonazepam (Klonopin) is useful for the management of myoclonic and atonic seizures. The usual dose is 0.05 to 0.3 mg/kg/d, given in two to four divided doses, with a therapeutic range of 0.02 to 0.08 µg/mL. Side effects include drowsiness, ataxia, and drooling [31,32].

Lamotrigine (Lamictal) is indicated for the management of partial, atonic, myoclonic, and tonic seizures, as well as Lennox-Gastaut syndrome. The maintenance dose ranges from 5 to 15 mg/kg/d, but because the drug interferes with other anticonvulsant agents, the dosage should be adjusted when used in conjunction with other antiepileptic medications. Lamictal should be initiated at low doses in patients who are also taking valproic acid and at higher doses when used in conjunction with phenytoin, carbamazepine, phenobarbital, or primidone. Lamictal is generally well tolerated, with most side effects being transient or dose-related, including GI upset, somnolence, dizziness, headache, and diplopia. The adverse effect of most concern is the development of a rash (Stevens-Johnson syndrome), which is especially common in patients who are also taking valproic acid [6,10,24,30,33].

Felbamate (Felbatol) is used mainly to treat intractable seizures that are refractory to other treatments, mainly the seizures of Lennox-Gastaut syndrome. The usual dose is 15 to 45 mg/kg, divided three to four times daily. It should be started at the low end of the dosage range and should be used as monotherapy because the risk of adverse effects is increased when it is used with other agents. Felbamate is known to increase the serum concentrations of phenobarbital, phenytoin, and valproic acid and to decrease that of carbamazepine. Side effects
include anorexia, nausea, vomiting, insomnia, and lethargy, with the major adverse effects of aplastic anemia and severe hepatotoxicity being reported as well. Children taking this medication should have blood counts and liver enzymes monitored frequently [6,10,30,33].

Gabapentin (Neurontin) is indicated for the management of partial and secondarily tonic-clonic seizures at a dose of 20 to 70 mg/kg/d. The dose should be given three to four times daily because of the drug’s short half-life. A major advantage of gabapentin is its lack of notable adverse effects. Minor side effects may include fatigue, dizziness, ataxia, and diarrhea. Increased appetite and weight gain may also occur [6,10,24,30,33].

Vigabatrin (Sabril) is effective for treating refractory partial seizures and infantile spasms. The maintenance dose is between 30 and 150 mg/kg/d, given once or twice daily. If seizures do not improve while on the drug, the patient is considered to be resistant to the drug. In some infants who have infantile spasms, treatment with vigabatrin resulted in the development of partial seizures, which is considered by some experts to be an improvement. The most impressive response has been seen in infants with tuberous sclerosis, with an efficacy similar to ACTH [10]. Side effects include weight gain, hyperactivity, and behavioral changes. The development of visual field constriction is a serious side effect that has limited the use of this drug [6,10,24,30].

Topiramate (Topamax) is indicated as adjunctive therapy in treating children with partial or generalized tonic-clonic seizures. It has also been effective in the treatment of Lennox-Gastaut syndrome, infantile spasms, and refractory complex partial seizures. The initial dose starts at 1 mg/kg/d, with a target maintenance dose of 3 to 9 mg/kg/d. The drug’s interaction with other anticonvulsant agents is minor. Topiramate produces several adverse effects of concern, with behavioral problems being the most common in children. Other side effects include anorexia, weight loss, sleep problems, fatigue, headache, diplopia, speech problems, and confusion. Nephrolithiasis is another serious effect of topiramate, and its use should be carefully considered in patients who have a history of kidney stones or those on a ketogenic diet [6,10,24,30,33].

Tiaagabine (Gabitril) is indicated as adjunctive therapy for managing refractory partial seizures. Dosing should begin at 0.1 mg/kg/d and be adjusted to a target dose of 0.5 to 1 mg/kg/d until adequate seizure control is achieved. Adverse effects are dose-related and more common with polytherapy. Reported side effects include fatigue, dizziness, headache, difficulty concentrating, and depressed mood [6,10,24,30,33].

Levetiracetam (Keppra) is effective as adjunctive therapy for refractory partial seizures in children aged 6 to 12 years of age. Usual maintenance doses range from 10 to 60 mg/kg/d. Adverse effects in the pediatric population include headache, anorexia, fatigue, and infection, including rhinitis, otitis media, gastroenteritis, and pharyngitis. Leukopenia has been reported in the adult literature but no such effect has been demonstrated in children [6,33].

Oxcarbazepine (Trileptal) is indicated as adjunctive therapy for treating partial seizures in children. Initial dosing begins at 5 mg/kg/d and is titrated upward,
as needed, to 45 mg/kg/d. Serum concentrations of phenobarbital and phenytoin may be increased when used in conjunction with oxcarbazepine. Adverse effects include somnolence, nausea, ataxia, diplopia, and a hypersensitivity rash. Approximately 25% of children who have had an allergic reaction to carbamazepine will develop a similar reaction to oxcarbazepine [6,33].

Zonisamide (Zonegran) is indicated as adjunctive therapy against partial seizures in children 16 years of age and older. It is also effective against generalized tonic-clonic, myoclonic, and atonic seizures as well as treatment for infantile spasms and Lennox-Gastaut syndrome. The initial dose is 2 to 4 mg/kg/d, given two or three times daily, with a maintenance range of 4 to 8 mg/kg/d. Common side effects include fatigue, GI upset, anorexia, ataxia, and rash. Adverse effects are more common early in the course of therapy and are less problematic with gradual dosage adjustments [6,33].

The ketogenic diet should be considered in children with refractory tonic, myoclonic, atonic, and atypical absence seizures whose seizures have failed to respond to standard anticonvulsant therapy. This diet has also been effective in the treatment of infantile spasms and Lennox-Gastaut syndrome. Studies have demonstrated a 50% to 70% reduction in seizures in children on the ketogenic diet [6,7]. The premise of therapy is that starvation will produce a ketosis that is associated with seizure reduction. The therapy is initiated with a 5- to 7-day inpatient hospital stay during which starvation is instituted until ketosis is achieved. Hypoglycemia is common during this starvation phase, and blood glucose levels must be aggressively monitored. Vomiting and dehydration may also occur during this initiation phase. A diet of 3 to 4 parts fat to 1 part carbohydrate and protein is then introduced. Vitamin and mineral deficiencies should be avoided with appropriate supplementation. Metabolic abnormalities that may develop include renal tubular acidosis, hypoproteinemia, and elevated lipids and hepatic and pancreatic enzymes. Other effects include infection and prolonged QT intervals. Therefore, an EKG and metabolic evaluation (including evaluation for inborn errors of metabolism) should be performed before initiating the diet. Laboratory studies should be monitored routinely during therapy as well [3,6,24].

Disposition

Well-appearing children may be managed following a first-time afebrile seizure on an outpatient basis, with the appropriate follow-up. Seizure first aid should be explained to the family before discharge. These children do not require anticonvulsant therapy, but they should be scheduled for EEG testing [3]. The overall recurrence rate in children with a first unprovoked afebrile seizure varies from 14% to 65%, with most recurrences seen in the first 2 years after the initial event [10,14]. The EEG has been found to be the most important predictor of recurrence, with a 2-year recurrence rate of 58% in patients who have an ab-
normal EEG result compared with a 28% seizure recurrence rate in patients who have a normal EEG result [34].

The decision to initiate drug therapy and the choice of anticonvulsant agent should be made in conjunction with the patient’s primary care provider and, oftentimes, in consultation with a neurologist [14]. These choices are complicated and should consider the risks associated with a seizure (recurrence, chance of injury, and psychosocial implications) against those of drug therapy (toxicity, effects on behavior and intelligence, and expense) [2,3]. Children with a prolonged seizure or postictal state or status epilepticus should be hospitalized for further observation and evaluation.

Special considerations

Neonatal seizures

It is often difficult in the newborn to differentiate between a seizure from other conditions, especially because newborns’ seizures can present in a variety of different ways, including apnea, subtle eye deviations, or abnormal chewing movements. In addition, associated autonomic system findings seen commonly with older seizure patients may not be apparent in neonates. A useful tip in differentiating between a newborn who has a seizure and a “jittery baby” is that true seizures cannot be suppressed by passive restraint, whereas seizures cannot be elicited by motion or startling [35].

The most common cause of a seizure in the first 3 days of life is perinatal hypoxia or anoxia. Approximately 50% to 65% of newborn seizures are caused by hypoxic-ischemic encephalopathy [36]. Intraventricular, subdural, and subarachnoid hemorrhages account for 15% of newborn seizures, and an additional 10% are caused by inborn errors of metabolism, sepsis, metabolic disorders, and toxins [37,38]. Pyridoxine deficiency is an autosomal recessive disorder that is a rare cause of newborn seizures and usually presents in the first 1 to 2 days of life [39]. These seizures will not respond to the usual therapy for status epilepticus but do respond readily to supplemental pyridoxine at a dose of 50 to 100 mg IV.

Benign familial neonatal convulsions and benign idiopathic neonatal convulsions are two types of neonatal seizures that carry a favorable prognosis. Benign familial neonatal convulsions typically present in the first 3 days of life in infants with a strong family history of epilepsy or neonatal seizures. The cause is unknown, but these seizures resolve by 1 to 6 months of age. Benign idiopathic neonatal convulsions, also known as “fifth day fits,” present on the fifth day of life and cease by day 15 of life [39].

The evaluation of neonatal seizures includes a thorough investigation for an underlying cause. Cranial imaging may consist of an ultrasonogram, a head CT, or MRI. Laboratory studies including electrolytes, glucose, calcium, magnesium, toxicology screen, urinalysis and culture, complete blood count and blood culture, and cerebrospinal fluid (CSF) studies should also be obtained. If an inborn
error of metabolism is suspected, then blood should be tested for amino acids, lactate, and pyruvate and ammonia levels, and urine should be tested for organic acids.

The immediate management of active neonatal seizures includes attention to the airway, breathing, and circulation and therapy to end the seizure. Benzodiazepines are often given as the first line of treatment but have been associated with serious adverse effects such as hypotension and respiratory depression in preterm and term infants, and therefore should be used with caution [38–40]. A long-acting anticonvulsant, usually phenobarbital, and then fosphenytoin are added [36]. Phenytoin is not a preferred initial agent because it has a depressive effect on the newborn myocardium and an unpredictable rate of metabolism in neonates because of immature hepatic function [38,39]. Topiramate and zonisamide are new agents that have also shown effectiveness in the treatment of neonatal seizures [35]. Pyridoxine or lidocaine may be used if refractory seizures are present [39]. If the seizure is a result of an electrolyte abnormality such as hyponatremia, hypocalcemia, or hypomagnesemia, then these abnormalities should be identified and treated rapidly. Ampicillin and either cefotaxime or gentamicin should be initiated in any patient who is suspected of having sepsis. Acyclovir also should be administered if there is a positive maternal history of herpes or the patient has a vesicular rash, focal neurologic findings, or a CSF pleocytosis or elevated CSF protein without organisms on Gram stain. Patients should be admitted to a monitored bed for further observation and evaluation [35].

**Febrile seizures**

Febrile seizures are the most common type of seizure in young children, with a 2% to 5% incidence of children experiencing at least one seizure before the age of 5 years [1,41]. A febrile seizure is defined as a convulsion that occurs in association with a febrile illness in children between 6 months and 5 years of age. A simple febrile seizure is single, brief (≤15 minutes), and generalized. A complex febrile seizure is much less common (approximately 20%) and is recurrent in a single illness (≥15 minutes), and focal.

The peak age for febrile convulsions is between 18 and 24 months. The exact pathophysiology is unknown, but it seems that a fever lowers the seizure threshold in susceptible children. It is unclear if the seizures are related to the rate of rise of the temperature or to the absolute peak sustained temperature [41–43]. A strong genetic predisposition exists, with a family history of febrile seizures present in 25% to 40% of children with febrile seizures [24].

Most febrile seizures are benign and self-limited, with no long-term neurologic or cognitive effects identified [41–43]. Approximately one third of children who experience a first febrile seizure will have at least one recurrence, and less than 10% of children will have more than three seizures. Most recurrences (75%) occur within 1 year of the initial episode. The younger the child is at the time of
the first seizure, the greater the likelihood of recurrence, with approximately 50% of children younger than 1 year of age having a recurrence [42]. Children who have higher temperatures at the time of the seizure have a lower likelihood of recurrence. A complex first febrile seizure neither alters the risk of recurrence nor predicts that recurrent seizures, if they occur, will be complex [1].

Febrile seizures occur in otherwise healthy children with no signs of meningitis, encephalitis, or other neurologic disorders. In these cases of typical febrile seizures, an extensive laboratory evaluation has been found to have low yield and is unnecessary [41]. Viral infections have been implicated in most cases in which a cause has been determined. Specifically, roseola infantum (human herpesvirus 6) and influenza A have been associated with an increased incidence of febrile seizures [44,45]. Children who have simple febrile seizures have the same risk for serious bacterial infections as children with fever alone [43,46,47].

In children younger than 1 year of age, clinical signs of meningitis may be subtle or lacking. Previous American Academy of Pediatrics guidelines recommended that a lumbar puncture (LP) be strongly considered in all infants less than 12 months of age and considered in those between 12 to 18 months of age [41]. However, a recent article [43] now recommends LP in infants less than 18 months of age only if the following are present: (1) a history of irritability, lethargy, or poor oral intake; (2) an abnormal appearance or mental status changes; (3) abnormal physical examination findings such as a bulging fontanelle, Brudzinski’s sign, or severe headache; (4) any complex seizure features; (5) slow postictal clearance of mental status; and (6) pretreatment with antibiotics. Therefore, performing routine LPs in children with simple febrile seizures may no longer be necessary. EEG and cranial imaging are not routine aspects of the evaluation of a simple febrile seizure. Further diagnostic tests (blood and urine studies) should be ordered only to investigate the source of the fever based on the child’s age and extent of the fever [41,46].

The treatment of a patient who presents during a febrile seizure is the same as for other seizure types. The initial priority should focus on stabilization of the airway, breathing, and circulation, with efforts then directed at terminating the seizure. The reduction of body temperature with antipyretics or other cooling methods should also be a part of the primary management. If the seizure persists, benzodiazepines are the first drug of choice. Phenytoin and phenobarbital may be used as second-line agents for persistent seizure activity [42].

Most febrile seizures, however, are brief, and patients will usually present for evaluation after the seizure activity has ceased spontaneously. For these patients, the issue of prophylactic medication therapy is controversial. The current consensus is that long-term medication therapy is not necessary for most patients who have simple febrile seizures. Following a febrile seizure, children with no other risk factors for epilepsy (a family history of epilepsy, a complex febrile seizure, or an underlying neurologic disorder) have only a 1% to 2% lifetime risk of developing epilepsy compared with a 0.5% to 1% risk in the general population [42]. In the presence of two or more of these risk factors, the future risk of developing epilepsy is 10%.
Prophylactic antipyretic therapy is not effective in reducing the risk of seizure recurrence. Anticonvulsant therapy may reduce recurrences but does not prevent the development of epilepsy. Most children with febrile seizures do not require anticonvulsant therapy. Phenobarbital has been used in the past for the long-term management of febrile seizures. To be effective, phenobarbital must be given continuously, not intermittently or at the onset of fever. Concerns about adverse behavioral and cognitive effects have limited its use. Valproic acid seems to be at least as effective as phenobarbital in preventing recurrent febrile seizures, but its association with severe hepatotoxicity in children less than 3 years of age has limited its use. Other agents, such as carbamazepine and phenytoin, are not effective in the prevention of recurrences. Oral or rectal diazepam, 0.5 mg/kg/d, given intermittently from the onset of fever has been shown to be as effective as continuous phenobarbital in preventing seizures [42]. Again, adverse effects (ataxia, lethargy, and irritability) may restrict the use of this therapy. Long-term prophylactic therapy may be considered in certain individualized cases.

Patients with a simple febrile seizure may be safely discharged to home with parental reassurance and seizure education. Those patients who have had a complex or prolonged seizure or required medication to terminate the seizure should be hospitalized.

References