

Seizures result from paroxysmal involuntary disturbance of brain function. The history and physical examination guide to management, and will help to differentiate seizures from non-epileptic disorders. The studies needed depend on the child's age, presence or absence of fever, the duration of seizure activity, and clinical examination. Afebrile seizures in children older than 6 months of age require minimal investigation, while younger children are more likely to have an electrolyte abnormality or hypoglycemia that requires treatment in the emergency department. Children with febrile seizures are not at high risk for serious bacterial illness and routine diagnostic evaluation of simple febrile seizures is not indicated. Anti-epileptic drugs should not be routinely initiated in the emergency department in children whose seizures have resolved. We review the management of status epilepticus in this paper.

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# Pediatric Seizures and Their Management in the Emergency Department

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**A** SEIZURE IS DEFINED as a paroxysmal involuntary disturbance of brain function resulting from excessive and abnormal discharge of cortical neurons. Clinical symptoms include impairment or loss of consciousness, abnormal motor activity, abnormal behavior, sensory disturbance, or autonomic dysfunction. Epilepsy refers to at least 2 or more unprovoked seizures occurring  $\geq 1$  day apart.

Seizures are either generalized or partial (focal). Generalized seizures can be absence, atonic, tonic-clonic, tonic, myoclonic, or infantile spasms. Partial seizures are classified as simple (simple partial), in which consciousness is preserved, or complex (complex partial), in which consciousness is impaired. Secondarily generalized seizures are partial seizures that become generalized.

## Seizure Pretenders

Paroxysmal nonepileptic disorders that may be mistaken for seizures include syncope, breath holding spells, sleep disorders, migraine headaches, apparent life threatening events (ALTE), and pseudoseizures. A pediatric epilepsy monitoring unit reported 15% of 883 children referred for epilepsy had paroxysmal nonepileptic events.<sup>1</sup>

Syncope refers to a sudden and transient loss of consciousness and postural tone due to briefly inadequate cerebral perfusion. The event is often preceded by lightheadedness, dizziness, nausea, or vomiting. The most common etiology in children and

adolescents is vasodepressor (vasovagal, neurocardiogenic, or reflex) syncope; an impaired ability to generate or maintain vasomotor tone is the underlying mechanism.<sup>2</sup> A history of cardiac disease, a syncopal event with no prodrome or occurring during exercise, loss of consciousness >5 minutes, or chest pain or palpitations suggests a primary cardiac cause, most commonly an arrhythmia. Congenital long QT syndrome should be suspected if there is a history of frequent syncope, a family history of syncope, or family history of early cardiac death.<sup>3</sup> When syncope and a brief seizure occur within 20 seconds of asystole, this is known as Stokes-Adams syndrome.<sup>4</sup>

Breath-holding spells have been reported to occur in 0.1% to 4.6% of well children.<sup>5,6</sup> The spells are generally benign, involuntary, and reflexive, and begin with a provocation resulting in crying.<sup>7</sup> The diagnosis is based on the distinctive sequence of events: crying, noiseless state of expiration, color change, and loss of consciousness and postural tone. Occasionally there is body jerking and urinary incontinence.<sup>8</sup> Depending on the color of the child during the episode, the spells are classified as cyanotic or pallid. Virtually all breath-holders have their first attack by 2 years of age.<sup>8</sup> The frequency varies from once per year to several per day, and cease in 50% of children by 4 years of age, and in almost all by the age of 8. There is often a history of breath-holding spells in first degree relatives.<sup>6,8</sup>

Sleep disorders include night terrors, nightmares, and narcolepsy. Night terrors occur during partial arousal from deep non-REM sleep. The classical description of a night terror involves a 2- to 6-year-old child who awakens suddenly within 4 hours of falling asleep, appears frightened or confused, and cries inconsolably for 10 to 15 minutes. The child is diaphoretic, tachycardic, and tachypneic.<sup>9</sup> The episode resolves with the child falling asleep. Upon awakening the next morning, the child is amnesic to the event. Nightmares, which affect approximately 30% of children aged 5 to 12 years, are vivid and terrifying nocturnal episodes in which the dreamer is abruptly awakened from REM sleep, and is able to describe a detailed and often bizarre dream plot. Narcolepsy is a disorder characterized by cataplexy (sudden loss of muscle tone with preservation of consciousness), sleep paralysis (inability to move during awakening or onset of sleep), hypnagogic hallucinations (hallucinations occurring at sleep onset) and frequent daytime naps.<sup>10,11</sup> It usually starts in adolescence, but its onset may be as early as 3 years of age.<sup>12</sup> Sleep studies are required for a definitive diagnosis.

Migraine headaches may mimic seizures, particularly when accompanied by an aura, motor dysfunction, or clouding of consciousness. Complicated migraine with hemiparesis can be mistaken for postictal paralysis. A history of migraine headaches and a normal level of consciousness help to distinguish migraines from seizures. In addition, migraine-related visual phenomena tend to last longer than those resulting from occipital seizures, and migraine-associated numbness and tingling is of longer duration than are the sensory seizures of parietal lobe origin.

An ALTE is an episode characterized by some combination of apnea, color change, choking, gagging, and loss of muscle tone. Apnea of infancy is defined by the duration of the apnea, 20 seconds or longer, or a shorter pause associated with bradycardia, cyanosis, pallor, or marked hypotonia.<sup>13</sup> Mothers of infants who suffer sudden infant death syndrome report an ALTE more frequently than do controls.<sup>14</sup> The median age of occurrence of an ALTE is 2 months. In 1 series of infants hospitalized for ALTE (n = 163), 37% had a discharge diagnosis of seizure, suggesting significant clinical overlap between the two. Eighteen percent had a diagnosis of gastroesophageal reflux, and 9% a diagnosis of apnea.<sup>15</sup>

Pseudoseizures are an expression of psychologic conflict and are considered to be a conversion disorder. They most commonly occur in teenage girls and usually consist of thrashing bilateral motor activity.<sup>16,17</sup> Often the patient has an underlying seizure disorder or a family history of seizures.<sup>17,18</sup> The patient will resist forced opening of the eyelids and avoids noxious stimuli such as sternal massage or smelling salts. Pseudoseizures tend to be longer than epilepsy-related seizures.<sup>19</sup> Although episodes may include falling to the ground or violent thrashing, children with pseudoseizures rarely injure themselves.<sup>16</sup> Despite these differences, it can be quite difficult for clinicians to distinguish pseudoseizures from epilepsy using clinical features alone.<sup>16,20</sup>

### Clinical Approach to the Child With a Non-Febrile Seizure

A thorough history is crucial to determining if a seizure occurred. Information is needed about possible precipitating factors including fever, trauma, or ingestion (toxin or drug), as well as prior medical and family histories. Witnesses should be asked to describe the event in detail: the types of motor and eye movements (eyes/head turned to the side), ev-

idence of aimless behavior (automatisms), slurring of words, changes in breathing or skin color, change in consciousness, incontinence, duration of the event, and the presence of a post-ictal period.

The physical exam is used to identify a possible etiology for the seizure. Vital signs are helpful, and the head should be evaluated for trauma. The eye examination should include pupil size and reactivity, extraocular movements, and funduscopy; retinal hemorrhages suggest intentional injury.<sup>21</sup> Febrile children should be examined for meningeal signs. The skin should be examined for pigmentation or rashes, evidence of neurocutaneous syndromes, or infection. A detailed neurologic examination must be performed. Serial examinations should demonstrate a transition from the postictal state to the child's normal level of consciousness.

Routine laboratory investigation in healthy children over 6 months of age has not been shown to be helpful in identifying the cause of seizures; thus in the absence of a history of illness, vomiting or diarrhea, or suspected ingestion, they are not needed.<sup>22-24</sup> As some seizures in infants younger than 6 months old are associated with hyponatremia or hypocalcemia, serum sodium, calcium and magnesium levels should be considered for these infants.<sup>25,26</sup> Hypoglycemia is highly associated with seizure activity; a rapid assay for glucose performed at the bedside may be diagnostic and can direct therapy. Otherwise, individual clinical circumstance or the failure to return to baseline alertness should guide laboratory testing. Toxicology screening should be considered if there is suspicion of toxin exposure.<sup>27</sup>

There is no evidence to indicate that lumbar puncture should be routinely performed on a child with an afebrile seizure.<sup>28</sup> Among children with persistent alteration of mental status of unknown etiology or meningeal signs, particularly if associated with fever, a lumbar puncture should be considered for the evaluation of meningitis or encephalitis. Head imaging should be performed prior to lumbar puncture if signs of elevated intracranial pressure or Cushing's triad (bradycardia, hypertension, and hypopnea) are present.

Although neuro-imaging studies detect abnormalities in up to one-third of children with first time afebrile seizures, a review of data from well-designed studies suggested that approximately 2% were of clinical relevance. Thus, the recommendation in the practice parameter "Evaluating the first nonfebrile seizure in children" is that routine neuro-imaging not be performed.<sup>22</sup>

A more recent study of children with new-onset afebrile seizures (n = 500 consecutive cases), 95% of whom underwent neuro-imaging, reported that 2% of children designated to be low risk by partition analysis had an abnormality detected with neuro-imaging that was of clinical relevance. Of note, the partition analysis did not include a normal neurologic examination as part of the low risk criteria; had that been included, the incidence of an abnormality detected by neuro-imaging would have been even lower.<sup>29</sup> A computed tomography (CT) scan should be strongly considered in children with risk factors including head trauma, focal (partial) seizure, seizure longer than 15 minutes, focal postictal deficits not rapidly resolving (Todd's paralysis), persistently altered level of consciousness, sickle cell disease, bleeding disorders, malignancy, and human immunodeficiency virus infection.<sup>29-33</sup>

Magnetic resonance imaging (MRI) is more sensitive than CT to detect subtle etiologies of seizures such as atrophy, dysgenesis, dysplasia, infarction, trauma, tumors, and vascular malformations. Non-urgent MRI study should be considered in several patient groups: children less than 1 year old, those with focal seizures, and children with unexplained neurologic abnormalities or undiagnosed cognitive or motor impairments.<sup>34,35</sup>

In a child with a new-onset seizure, an electroencephalogram (EEG) may help to differentiate ictal from non-ictal events, to determine seizure type or epilepsy syndrome, and to better define the risk for recurrence. For most children, it is not necessary to perform the EEG as part of the initial emergency department (ED) evaluation. In fact, if it is performed shortly after the seizure (<48 hours), the EEG may show diffuse postictal slowing without prognostic significance.<sup>22,36-39</sup> Among children with persistent altered mental status after a seizure, an emergent EEG is helpful to identify subtle or nonconvulsive status epilepticus (SE).<sup>39</sup>

Although many children have just 1 unprovoked seizure, approximately 40% have a recurrence. Children in whom there is no suspicion of trauma, infection, or intoxication and who have returned to their baseline state may be discharged with appropriate medical follow up, including an EEG. Anti-epileptic drugs (AED) are usually not prescribed. Discharge instructions should describe what to do if the seizure recurs.

AEDs control seizures by either lowering the excitability of the neuronal pacemaker pool, or by suppressing the spread of the spike bursts. Generalized tonic-clonic seizures may be controlled with valproic acid, phenytoin, phenobarbital, carbamazepine, and primidone. Carbamazepine and phenyt-

oin are the drugs of choice for partial seizures; absence seizures are treated with ethosuximide. Much is known about the established AEDs, including clinical pharmacokinetics, and potential dose-related and idiosyncratic toxic effects. Newer agents, including gabapentin, lamotrigine, topiramate, tiagabine, and vigabatrin are used when seizure control is not achieved with an established AED.<sup>40</sup>

### Clinical Approach to the Child With a Febrile Seizure

Febrile seizures are the most common convulsive disorder of childhood. Approximately 3% to 5% of children will experience a febrile seizure before their fifth birthday, with the peak onset in the second year of life.<sup>40,41</sup> Approximately two-thirds of the patients are male with a median age of onset of 19 to 23 months. The risk of febrile seizure increases when there is a history of febrile seizures in first-degree relatives, as does the risk of recurrence. Children with high fevers and chills may be mistakenly identified as having had a febrile seizure. Often, a carefully taken history, with the clinician demonstrating the rhythmic movements associated with clonic seizures in contrast to the tremulous nature of chills, may help distinguish between the two.

Febrile seizures are defined as those that occur in febrile children 6 months to 5 years of age who do not have evidence of intracranial infection or known seizure disorder. Thus, children with febrile seizures are a distinct patient group from children with epilepsy who have an intercurrent febrile illness. Eighty percent of febrile seizures are simple (generalized, lasting less than 15 minutes, or occurring only once in a 24-hour period), carry few risks of complications, and have excellent short- and long-term prognoses. Children whose seizures have focal features, last more than 15 minutes, or occur more than once in a 24-hour period are classified as having complex febrile seizures.

As most febrile seizures occur during the first 24 hours of illness, the seizure is the first sign of a febrile illness in approximately 25% to 50% of cases. Although children with febrile seizures have high mean temperatures (39.8°C), they are not at high risk for serious bacterial illness. In a multi-center retrospective review of patients with first time simple febrile seizures (n = 455), bacteremia occurred in 1.3% (95% CI: 0.1%-2.5%) of children in whom blood cultures were drawn.<sup>42</sup> This is similar to bacteremia rates among febrile children reported in other studies completed after widespread use of the

*Haemophilus influenzae* vaccine.<sup>43,44</sup> In the multi-center review, the most common associated infectious illnesses were otitis media (34%), upper respiratory infection (12%), viral syndrome (6%), and pneumonia (6%). Urinary tract infection (3%), gastroenteritis (2%), varicella (2%), and bronchiolitis (1%) were identified in a smaller subset of patients. Thirty-four percent of patients had no infectious diagnosis at time of ED discharge, presumably because they were early in their course of illness.<sup>42</sup>

A careful history and physical exam to identify the source of the fever and evidence of trauma is important. Current evidence suggests that routine diagnostic evaluation of children with simple febrile seizures is not indicated. Based on age and height of fever, children with fever without a source should be evaluated for urinary tract infection. Children who have been pre-treated with antibiotics, who have focal seizures, or whose seizures occur after several days of illness should be carefully evaluated and further diagnostic evaluation should be directed by their histories and physical exams.

In patients whose level of consciousness has not returned to baseline or who are lethargic or irritable, lumbar puncture should be performed to exclude meningitis. Children who are younger than 6 months of age, and thus fail age criteria for febrile seizures, warrant a more careful evaluation, with attention to metabolic derangements, possible underlying neurologic disorders, and meningitis or encephalitis. Aseptic meningitis rarely presents with a febrile seizure unaccompanied by other signs; retrospective data suggest it was never the sole presenting sign in patients with bacterial meningitis.<sup>45</sup> The clinician's decision to perform a lumbar puncture will vary based on individual patient characteristics, the accessibility of follow-up, the clinician's judgment about the risks and benefits of tests, and his or her confidence in managing infants and young children.

An EEG is not usually indicated for evaluation either in the ED or as an outpatient. Neuro-imaging should be obtained on those children who have a focal seizure, focal neurological findings, history of head trauma, or failure to return to baseline neurologic status.

Antibiotics are indicated for focal infections; AED therapy is not indicated.<sup>46</sup> Oral diazepam prophylaxis was shown in one study to be effective in decreasing the recurrence rate of febrile seizures in a select high-risk population; other studies have failed to reproduce the results, largely because of non-compliance.<sup>47,48</sup> Although the data are somewhat limited, antipyretics have not been shown to

be effective in preventing the recurrence of febrile seizures. Thus, the practice of using "round the clock" acetaminophen or ibuprofen is not supported in the literature and may contribute to parental fever phobia.<sup>49</sup>

Approximately one-third of children with febrile seizures have a recurrence; an estimated half of those will have an additional recurrence. Age younger than 18 months at the time of the first seizure and a history of febrile seizures in first-degree relatives are associated with an increased risk of recurrence. Although children with complex febrile seizures as first seizures have been identified as being at increased risk for recurrence, other data suggests this does not place children at higher risk.<sup>50,51</sup>

### Neonatal Seizures

Neonatal seizures occur in an estimated 2 per 1,000 live births, with higher rates among low birth weight or premature infants. Most occur within the first week of life, with the majority of these occurring within the first few days. When compared to those among older children, neonatal seizures are less often idiopathic. Among term infants who develop seizures on days 3 to 10 of life, causes include intracranial hemorrhage, metabolic derangements (inborn errors of metabolism, pyridoxine deficiency, hypocalcemia, hypoglycemia, or hypo- or hypernatremia), intracranial infection, developmental cerebral abnormalities, and neonatal epilepsy syndromes. Most neonatal seizures are identified by unusual repetitive and stereotypic movements; however, seizures are often quite difficult to distinguish from jitteriness or other benign movements among neonates. When compared to those in older children, neonatal seizures have some unique features, including multifocality, asynchrony of clonic activity, and the lack of generalized tonic-clonic seizures.<sup>52</sup>

The history should include information about the pregnancy, labor and delivery, maternal risk factors for infection, prior stillbirths or deaths in neonates, and feeding history. The physical examination should include head circumference, and close observation for dysmorphic features and cutaneous lesions. Laboratory investigations that should be strongly considered include serum glucose, calcium, magnesium, pH, sodium, sodium bicarbonate, blood urea nitrogen, and ammonia. Additional laboratory studies that may be helpful include serum amino acids, lactate and urine organic acids, studies of hepatic function, chro-

mosome karyotype, and viral studies. Lumbar puncture should be considered to determine the presence of infection or intracranial hemorrhage. CT scanning can usually be completed quickly and will identify gross congenital brain anomalies, hemorrhage, and intracranial calcifications; a limitation of CT is that if performed early after an infarct, the infarct may be missed. MRI requires more time but provides high resolution, and thus may be of greater yield.

The treatment of neonatal seizures is directed to correcting the underlying cause. Ventilation and perfusion should be supported as needed. The AEDs typically used in the acute treatment of neonatal seizures are phenobarbital (20 mg/kg as a loading dose, followed by additional increments of 10 mg/kg as required to achieve serum levels between 20 to 40 micrograms/mL), phenytoin (20 mg/kg as a loading dose to achieve serum levels between 15 to 20 micrograms/mL), and a benzodiazepine given intravenously. The combination of a benzodiazepine and phenobarbital in a neonate carries a significant risk of respiratory depression. Pharmacokinetic data suggest that metabolism in neonates is similar to that in older children; thus, fosphenytoin is likely to be as efficacious as phenytoin with fewer potential risks.<sup>53,54</sup>

### Post-Traumatic Seizures

Post-traumatic seizures can occur as an acute result of blunt or penetrating head trauma and as post-traumatic sequelae. Early post-traumatic seizures are defined as those occurring within 1 week of the injury, whereas late post-traumatic seizures occur after 1 week. While population-based data are limited, these seizures have been reported to occur in as many as 15% of children after head injury. Early post-traumatic seizures are associated with cerebral edema, epidural, subdural, and intracerebral hematomas, and traumatic subarachnoid hemorrhages.<sup>55</sup> They do not appear to be associated with epilepsy.<sup>56</sup> Impact seizures occur within 1 to 2 hours of head trauma; unlike early post-traumatic seizures, impact seizures do not appear to be associated with severe injury.

### Status Epilepticus

Although most seizures in children stop prior to arrival at a hospital, an estimated 60,000 US children are treated each year for status epilepticus (SE). A third of the episodes will be the initial event in a patient with new onset epilepsy and an addi-

TABLE 1. Seizure Etiology by Age of Onset

6 Months-3 Years	> 3 Years
Febrile seizures	Idiopathic
Birth injury	Infection
Infection	Trauma
Toxin	Cerebral degenerative disease
Trauma	
Metabolic disorder	
Cerebral degenerative disease	

tional third occur in children with established epilepsy. Other etiologies include atypical febrile seizures, acute neurologic conditions (meningitis, encephalitis, trauma, tumors, stroke), intoxications, and degenerative or progressive neurologic conditions (Table 1).<sup>57,58</sup> Up to 70% of children with epilepsy beginning before age 1 will experience an episode of SE in their lifetime.<sup>59</sup> The outcome of status is primarily a function of the underlying etiology and when aggressively treated, the incidence of sequelae in children without an underlying neurologic insult is small. The mortality rate related to a prolonged seizure in children is estimated to be 1% to 3%.<sup>58-60</sup> Seizure duration of greater than 1 hour, especially with hypoxia, has been associated with permanent neurologic injury.

The World Health Organization defines SE as "a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying or enduring epileptic condition."<sup>61</sup> As this definition is not clinically useful, most clinicians and researchers define SE to be continuous or repetitive seizure activity of at least 30 minutes with failure to regain consciousness between convulsions.<sup>59</sup> As almost all self-limited seizures stop within 5 minutes, the Working Group on SE of the Epilepsy Foundation of America recommends that any patient with seizure duration of longer than 10 minutes have AED therapy initiated.<sup>62</sup> This includes most children presenting to the ED with ongoing seizure activity.

As much of the morbidity associated with SE can be attributed to hypoxia, supportive efforts, seizure management, and diagnostic work-up all need to occur simultaneously. The hypoxia associated with SE is multifactorial: impaired mechanical ventilation secondary to tonic-clonic activity, increased salivation, increased tracheobronchial secretions,

and increased oxygen consumption resulting from the seizure. The acidosis of SE is of both respiratory and metabolic origins, as seizure activity results in increased metabolic needs unmet by tissue oxygenation and perfusion, causing lactic acidosis.

In the first 30 minutes of seizure activity, catecholamine release results in an increase in heart rate, blood pressure, central venous pressure, cerebral blood flow, and serum glucose. After 30 minutes of generalized tonic-clonic activity, blood pressure begins to drop, and cerebral blood flow, although still increased above baseline, drops to the point where it may be unable to supply adequate substrate and oxygen to meet increased cerebral metabolic demands. This results in impaired cortical oxygenation. Additional systemic effects of prolonged seizure activity include increase in body temperature, decrease in serum glucose, an increase in serum potassium level, and an increase in creatine phosphokinase. As a result of muscle breakdown, myoglobinuria, and acute renal failure may develop.

The goals of management are to maintain adequate vital function so as to prevent systemic and cerebral hypoxia as well as other systemic complications; to terminate the seizure activity as quickly as possible, while minimizing morbidity from treatment; and to evaluate and treat the underlying cause of SE. There is a risk of respiratory failure resulting from seizure activity, the medications used to terminate seizures, and from postictal hypoventilation. Positioning alternatives include supine on the bed with the head in midline or left lateral decubitus to prevent aspiration of emesis. Upper airway obstruction can be managed with airway positioning using a neck roll, a jaw thrust maneuver, or the placement of an oral or nasal airway. 100% oxygen via a non-rebreather mask should be initiated in all patients. Suction equipment and an appropriately sized bag-valve-mask device should be immediately available.

Consider bag-valve-mask ventilation or intubation if there is significant respiratory compromise. An intravenous line (IV) should be placed and blood drawn; a bedside glucose test should also be done. If hypoglycemic, 0.5 mg/kg of glucose should be given as a bolus, either as 2 cc/kg of 25% dextrose in water, or 5 cc/kg of 10% dextrose in water. A directed history should be obtained: age, a history of prior seizures, AED therapy, and recent fever, illness, injury, or ingestion. Normal saline is compatible with all anticonvulsants and it should be used unless the child is hypoglycemic. If IV access cannot be obtained quickly, rectal or intramuscular (IM) routes can be used to administer anticonvul-

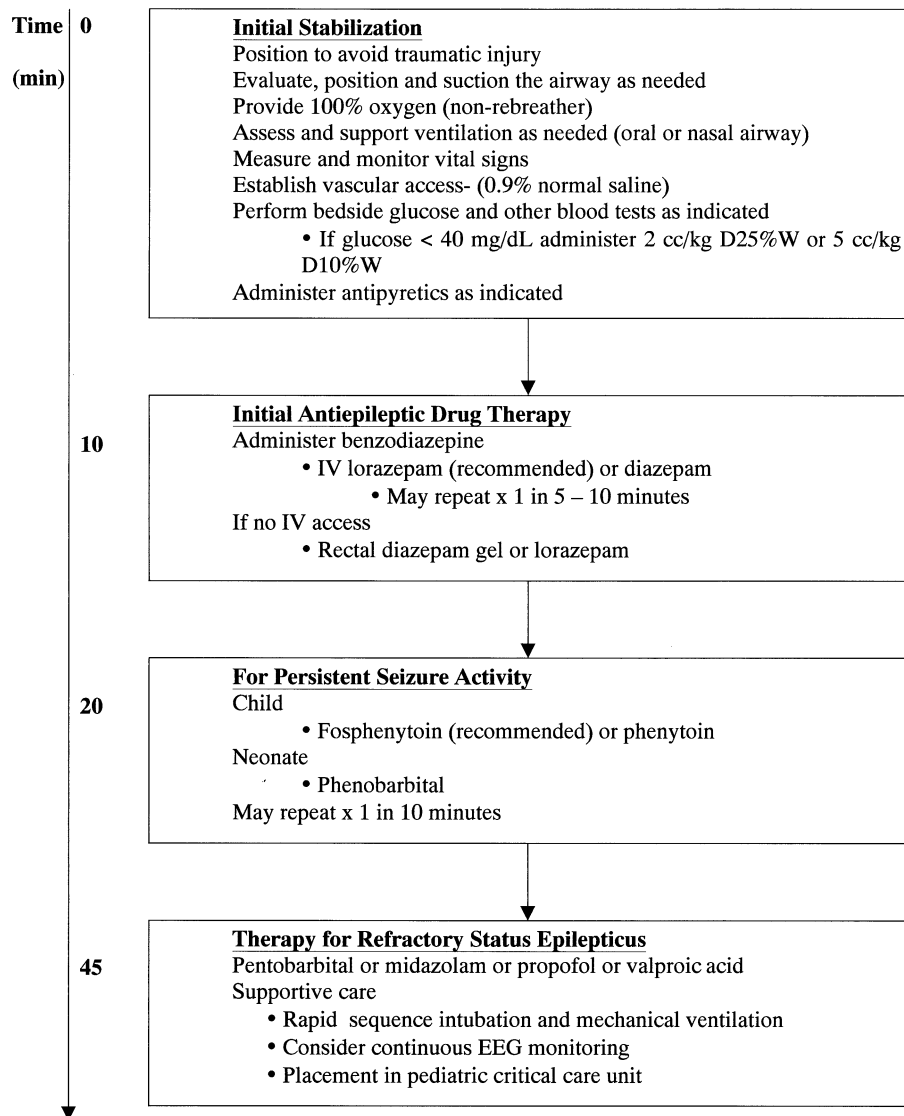


Figure 1. Time management scheme for status epilepticus.

sant medications. If necessary, the intraosseous route may be used. A management pathway is described in Figure 1.

Benzodiazepines are the initial treatment for SE, as they act rapidly and are highly effective in terminating seizure activity (Table 2). One or 2 doses, administered 5 minutes apart, will be effective for most children. Drugs in this class can cause hypotension and respiratory depression, which can be minimized by slowing drug infusion rates and waiting an appropriate period of time before giving additional doses. Both lorazepam and diazepam have a rapid onset of action; the median times to end of seizure is 2 and 3 minutes respectively. Lorazepam has a smaller volume of distribution and a much longer duration of action. Effective brain levels can

continue for 12 to 24 hours. Limited data suggest lorazepam is associated with somewhat less respiratory depression among children than diazepam. In one study, 3% of children ( $n = 86$ ) treated with lorazepam were treated with an additional AED and 3% had respiratory depression, versus 31% and 15% respectively for diazepam.<sup>63,64</sup> In a randomized, double blind trial in adults ( $n = 205$ ), lorazepam was somewhat more effective than diazepam in terminating seizures (59% vs 43%); each had a 10% incidence of respiratory or circulatory complications.<sup>65</sup> Because of its longer duration of action, lorazepam is favored as the initial treatment of SE in children at most centers.<sup>66</sup> When diazepam is used for SE, it should be followed by a long-acting AED, such as fosphenytoin.

TABLE 2. Drugs Used to Terminate Status Epilepticus

Drug	Dose	Max Dose	Onset of Action	Duration of Action	Maximal Rate of Administration
Lorazepam	0.05-0.1 mg/kg IV or PR	4 mg	2-3 min	12-24 hrs	<2 mg/min
Diazepam	0.1-0.3 mg/kg IV or 0.5 mg/kg PR	10 mg	1-3 min	5-15 min	<2 mg/min
Phenytoin	20 mg/kg	1000 mg	10-30 min†	12-24 hrs	<1 mg/kg/min; <50 mg/min
Fosphenytoin	20 mg/kg PE	1000 mg	10-30 min†	12-24 hrs	<3 mg/kg/min; <150 mg/min
Phenobarbital	20 mg/kg	1000 mg	10-20 min	1-3 days	<1-2 mg/kg/min; <100 mg/min

Abbreviation: PE, Phenytoin equivalents.

†After infusion.

In the absence of IV access, lorazepam may be administered via the rectum. A diazepam gel (Diastat) has also been developed for rectal use. The rectal form has consistent and rapid absorption, less respiratory depression than the IV form, and is easy to administer.<sup>67</sup> It is a good medication to use both at home and in the field to safely terminate seizure clusters or SE. A retrospective effectiveness study of rectal versus IV diazepam use among pre-hospital personnel demonstrated successful seizure termination rates of 81% and 100% respectively. Recurrences occurred prior to ED arrival in 31% (rectal) and 60% (IV) of the children; 2 children in the IV group were intubated.<sup>68</sup> Seizure recurrence, often within 15 to 20 minutes, results from diazepam's extensive distribution to peripheral fat stores.

Midazolam, a water soluble benzodiazepine, is effective when administered IM, whereas lorazepam and diazepam are prone to slow, erratic absorption and significant local discomfort.<sup>66</sup> A prospective randomized trial (n = 24 children) found IV diazepam (0.3 mg/kg) and IM midazolam (0.2 mg/kg) to be equally effective in stopping seizures; seizures were stopped faster in the IM midazolam group.<sup>69</sup> Midazolam has also been demonstrated to be effective in terminating seizures when administered buccally and intranasally.<sup>70,71</sup>

Although particularly important among children treated with diazepam, a long-acting AED should be considered for all children who present in SE. Fosphenytoin is a prodrug of phenytoin, which is rapidly replacing the parent compound. Fosphenytoin lacks the ethylene glycol base used as a diluent for phenytoin: this reduces the tissue toxicity and the cardiac side effects (hypotension, arrhythmia, and asystole). It is compatible with any IV solution and

can be hung with dextrose, it can be infused more rapidly, and it can be given via the IM route if necessary.<sup>72,73</sup> The dose is expressed as phenytoin sodium equivalents (PE), and is 15 to 20 PE/kg. An additional 10 PE/kg may be administered as needed to stop seizure activity. The maximum infusion rate is 150 PE/min.<sup>74</sup> The disadvantages of fosphenytoin include limited pediatric experience and high cost. An economic outcome evaluation found its use to likely result in an overall institutional cost savings relative to the use of phenytoin.<sup>75</sup>

Phenobarbital is used for the control of seizures in neonates, as an alternative to phenytoin/fosphenytoin, and in patients who do not respond to phenytoin/fosphenytoin. It is less lipid-soluble than benzodiazepines and phenytoin and thus takes longer to stop a seizure (15 to 30 min). Due to its long elimination half-life, therapeutic effects persist for up to 48 hours. The loading dose, administered IV or IM, is 20 mg/kg administered at a rate of 1 mg/kg/min.<sup>76</sup> Its side effects, sedation and cardiorespiratory depression, are amplified when combined with benzodiazepines.<sup>76</sup> It is contraindicated in patients with hypersensitivity to barbiturates and in individuals with porphyria.

Many consider SE to be "refractory" when the patient fails to respond to sequential treatment with a benzodiazepine, phenytoin/fosphenytoin, and phenobarbital. Aggressive intervention with high-dose barbiturates or benzodiazepines is indicated and requires intensive care support, intubation and mechanical ventilation, and paralysis and EEG monitoring.<sup>77,78</sup> The outcome depends on the etiology as well as the duration of uncontrolled SE.<sup>79</sup>

There is no consensus as to the optimal therapy for refractory SE (Table 3). Pentobarbital, a short acting barbiturate, can be used.<sup>80,81</sup> This rapidly

TABLE 3. Drugs Used for Refractory Status Epilepticus

Drug	Loading Dose	IV drip	Side Effects	Neurologic Recovery
Midazolam	0.15-0.2 mg/kg IV	0.1-0.3 mg/kg/hr	Somnolence, respiratory depression	Quick
Pentobarbital	5-15 mg/kg IV	0.5-5 mcg/kg/hr	Hypotension, myocardial depression, low cardiac output	Slow
Propofol	1-3 mg/kg/hr IV	2-10 mg/kg/hr	Bradycardia, apnea, hypotension with fast infusion	Quick
Valproic Acid	15-20 mg/kg IV over 1-5 min, Max 40 mg/kg	5 mg/kg/hr	No significant local or cardiovascular side effects reported to date	Quick

results in an EEG burst suppression pattern and a reduction in cerebral metabolic rate.<sup>78</sup> Decerebrate posturing has been noted to occur concurrent with the onset of the burst suppression pattern. There are significant complications associated with this drug including hypotension, myocardial depression, low cardiac output, and post-infusion weakness.

Midazolam, a water-soluble benzodiazepine, has been shown to be effective in terminating refractory SE.<sup>82-84</sup> It is lipophilic at physiologic pH, has a rapid onset of action, quickly passes the blood-brain barrier, and causes minimal cardiorespiratory depression.<sup>84,85</sup>

Propofol is another highly effective, lipid-soluble drug. It is a non-barbiturate anesthetic with hypnotic and anticonvulsant properties. It has a rapid onset of action and quick recovery times. A few case reports and small studies have been successful in using it as an IV bolus, followed by a continuous infusion titrated to cessation of seizure activity or inducement of burst suppression. Known side effects include bradycardia, apnea, and hypotension with rapid infusion. It has less cardiorespiratory depression than pentobarbital. Some case reports have described unexplained acidosis; thus, this drug is currently not used for sedation, and further study is warranted.

Valproic acid, now available in an IV preparation, has recently been approved by the FDA for use in SE. The drug is known to be effective in both partial and generalized epilepsy syndromes in childhood, and now that it is available in an IV preparation can be given as a single dose (15 to 20 mg/kg) as well as a continuous infusion (5 mg/kg/hr).<sup>81</sup> The initial dose may be repeated up to a maximum of 40 mg/kg. In one study involving 41 children, SE was successfully terminated in 78% of

cases with this approach. Two-thirds of the patients responded within 6 minutes of the initial dose. The drug was well tolerated with no systemic or local side effects, and the response rate was dose-related.<sup>86</sup> The advantages of valproic acid are that it is significantly less sedating than the other drugs used for refractory SE and it has an excellent cardiovascular profile. Although clinical trials to date have been limited, it appears that valproic acid should be considered prior to the use of general anesthesia and barbiturate coma.

### Nonconvulsive Status Epilepticus (Absence Status, Partial Complex Status)

Absence SE is the most common form of nonconvulsive SE and may be the presenting feature in a child with absence or intractable mixed generalized epilepsy. Children with absence SE demonstrate partial responsiveness with prolonged confusion, disorientation, a paucity of speech, and a generalized EEG epileptiform alteration. Complex partial SE usually presents with altered mentation associated with stereotyped automatisms and wandering eye movements. EEG plays an essential role in establishing these diagnoses.<sup>87</sup>

Since absence SE does not result in altered vital signs, acidosis, or hypoxia, its recognition and treatment is considered to be urgent, but not emergent.<sup>79</sup> The administration of a benzodiazepine usually results in the rapid termination of both absence and partial complex SE.<sup>79</sup> The timely recognition and treatment of complex partial SE is more urgent, as the duration of the seizure may affect the neurologic outcome.<sup>87,88</sup> The drugs used are the same as for generalized SE.

## Summary

Seizures are caused by a paroxysmal involuntary disturbance of brain function. Several nonepileptic disorders may be mistaken for seizures. In children with afebrile seizures, serum electrolytes and glucose should be strongly considered if the child is < 6 months of age. For most children, neuro-imaging in the ED is not indicated; it should be considered in those with risk factors including chronic illness, trauma, or prolonged or focal seizures. Emergent EEG is helpful in those with persistent altered mental status. Neonatal seizures require a more comprehensive work-up for metabolic disease, infection, and central nervous system abnormalities. Children with febrile seizures are not at high risk for serious bacterial illness and routine diagnostic evaluation of simple febrile seizures is not indicated. Anti-epileptic drugs should not be routinely initiated in the ED. Benzodiazepines are the initial treatment for status epilepticus, followed by a long-acting anti-epileptic drug such as fosphenytoin.

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