Pediatric Seizures

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KEYWORDS

- Seizures • Febrile seizures • New-onset seizures • Neonatal seizures • Pediatric
- Ketogenic diet • Status epilepticus

KEY POINTS

- Neonatal seizures may often be subtle but still have a high correlation with significant pathologic conditions.
- Because patients who have had a simple febrile seizure are at no greater risk for having meningitis than those who have a fever without a seizure, the evaluation of a simple febrile seizure should focus on an age-appropriate evaluation of the fever, and the management should include appropriate anticipatory guidance and education for the family.
- Complex febrile seizures include a vast spectrum of disease; therefore, the evaluation should be tailored to the individual case but with greater suspicion for potential central nervous system infection.
- Patients who have had a first-time afebrile seizure should have neuroimaging (with the preferred modality being magnetic resonance imaging), which can be performed as an outpatient if appropriate follow-up has been arranged.
- Emergent neuroimaging should be obtained in the emergency department after a new-onset seizure for those patients who have specific risk factors (eg, bleeding disorder, sickle cell disease, human immunodeficiency virus, head injury, ventriculoperitoneal shunt, age less than 6 months, focal seizure, prolonged postictal period, status epilepticus, and so forth).
- Status epilepticus becomes more refractory as seizure activity persists, so it should be aggressively treated. Standard algorithms for the management are still applicable, but new routes for administration of benzodiazepines and new second-line and third-line medications may be considered for use.

INTRODUCTION

Seizures represent the most common neurologic emergency of childhood and can be terrifying for patients and families. Although there are a variety of potential causes for seizures, the common pathophysiology entails abnormal electrical discharge of neurons; the extent of this aberrant electrical activity and subsequent manifestation of

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the seizure may range from subtle, nonconvulsive events to stereotypic movements to dramatic generalized convulsions. Additionally, the severity of a seizure can be varied, ranging from self-limited episodes without any hemodynamic compromise to prolonged events that may ultimately prove to be fatal in as many as 3% to 4% of patients.[1,2]

Seizures will affect 4% to 10% of children at some point during their lifetime, which translates to approximately 150,000 children in the United States experiencing a new-onset seizure annually.[3] About 10% of these new-onset pediatric seizures may present to the emergency department in status epilepticus.[4] Fortunately, of patients presenting with a new-onset seizure, only 30 000 will go on to develop epilepsy,[3] whereas the remainder will have manifested seizures secondary to other causes, such as fever, infection, or trauma. Those newly diagnosed with epilepsy will add to the 326,000 children residing in the United States who already carry a diagnosis of epilepsy undergoing various treatments ranging from medications to special diets to surgical interventions.[5] Given these numbers, it is critical for every emergency physician to be adept in the acute management of pediatric seizures and possess basic knowledge pertaining to pediatric epilepsy, its management, and potential complications.

SEIZURE MIMICS

Appropriate diagnosis of a seizure is critical to management. However, it is important to recognize that events that result in an altered level of consciousness or abnormal movements may not actually represent a seizure. A detailed history of the event by eyewitnesses (who may not always accompany patients to the emergency department) and a thorough physical examination of patients may yield an alternative diagnosis from a seizure. The differential diagnosis of seizurelike activity is broad but must be considered in all patients, even in those who carry a diagnosis of epilepsy (**Box 1**).

Infants and toddlers, who have developing nervous systems, may present with a myriad of diagnoses unique to their age group that may be interpreted by the family as a seizure. Parents can misinterpret the normal neonatal reflexes, particularly the startle reflex, as seizure activity. Additionally, they may exhibit jitteriness, which is characterized by symmetric tremor of the extremities with facial sparing; unlike seizure activity, these common movements can be stopped with gentle restraint.[6,7] During sleep, migrating myoclonic movements that do not disturb or wake the child may represent self-limited benign sleep myoclonus.[8] Additionally, shuddering attacks can cause concern with parents and consist of rapid shivering of the head, shoulder, and trunk as if cold water were dripping down the child's spine. These attacks may also have start in infancy and can persist through early childhood.[9] Severe gastro-esophageal reflex may manifest as Sandifer syndrome, which has also been misconstrued as seizures because of its associated back arching, crying, and writhing.

In addition, some common childhood behaviors can also mimic seizure activity. Breath-holding spells is a well-documented entity that can be seen in 5% of all children between 6 months and 5 years of age. They can have varied presentations, and some can seem to be associated with seizurelike activity. Breath-holding spells are associated with emotional stimuli or minor trauma and are brief, self-resolving, and without a postictal phase. They have an excellent prognosis with spontaneous remission with age.[10] In some children, families may also potentially interpret the rhythmic movements of self-gratification or stimulation as seizure activity.[11] Sleep disturbances, such as pavor nocturnus (night terrors), represent another category of seizure mimics in young children.

> **Box 1**
> **Differential diagnosis of seizures**
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> - Arrhythmia
> - Benign myoclonus of sleep
> - Breath-holding spells
> - Dystonic reaction
> - Hyperekplexia
> - Jitteriness
> - Migrainous syndromes (confusional, basilar)
> - Opsoclonus-myoclonus-ataxia syndrome (neuroblastoma)
> - Paroxysmal movement disorders
> - Psychiatric disorders (attention-deficit hyperactivity disorder, hysteria, rage attacks)
> - Psychogenic nonepileptic seizures (pseudoseizures)
> - Sandifer syndrome
> - Self-gratification disorder
> - Shuddering attacks
> - Sleep disorders (pavor nocturnus/night terrors, somnambulism/sleepwalking, narcolepsy)
> - Spasmus nutans
> - Syncope
> - Tics, stereotypies

Although some entities that mimic seizure activity can be caused by benign causes, others are associated with more concerning causes. Hyperekplexia (when infants have marked startling at sudden sounds or touch) may be so profound that it results in total body stiffening and apnea. Spasmus nutans is another entity that presents in children 4 to 12 months of age with pendular nystagmus, head nodding, and some head tilt or unusual head positioning. The rare syndrome of opsoclonus-myoclonus-ataxia that is associated with neuroblastoma may also be misconstrued as seizure activity.[8]

As children age, the differential diagnosis of seizurelike activity becomes similar to that of adults. New-onset narcolepsy, particular with regard to cataplexy, may raise concern for atonic (drop) seizures. Syncope may also be confused with seizures; in one study of patients with controlled initiation of ventricular arrhythmia, 65% of all patients had convulsive movements without an electrographic correlate of seizure activity.[12] Arrhythmia must be considered in any patient presenting with a concern for a new seizure.

One diagnosis that is difficult to differentiate from seizures is psychogenic nonepileptic seizures (PNES). This disorder may begin to present in early adolescence. These seizures are involuntary, physical expressions in response to psychological conflict from emotional, physical, or social distress.[13,14] Patients with PNES are overwhelmingly female, typically with psychiatric comorbidities, such as posttraumatic stress disorder, anxiety, or depression, and have had prior exposure to individuals with a history of seizures that serve as a model for seizurelike activity. Characteristics that are more suggestive of seizures include tongue biting, injury, bowel or bladder

incontinence, significant vital sign instability, cyanosis, altered pupillary responses, and postictal state.[15] Prolonged events in excess of 15 to 30 minutes; bizarre motor activity along the lines of thrashing, arching, or flailing; occurrence of events only in the presence of an audience; incorporation of verbal cues from bystanders; and brief or odd postictal states with crying or baby talking are more likely to represent PNES.[14] It can be particularly difficult to distinguish between PNES and true seizures because, in part, many individuals may suffer from both PNES and epilepsy. In some populations, accurate diagnosis may be delayed by a mean of 7 years with patients receiving aggressive antiepileptic therapy and other interventions for difficult-to-control epilepsy or recurrent cases of "refractory status epilepticus."[13]

NEONATAL SEIZURES

Although the previously mentioned entities and others can be inappropriately misconstrued as seizure activity, true seizures that occur in neonates (≤28 days of age) can often be misidentified as being benign. Neonatal seizures are not often as dramatic and clinically evident as seizures in older children and adults. Generalized tonic-clonic activity is rarely seen in neonates; instead, the neonate's immature nervous system and pattern of myelination generally leads to more subtle presentations of seizures.[16,17] Ocular movements, lip smacking, bicycling movements, and even apnea can be seizure presentations in neonates. Subtle seizure types account for approximately 50% of all neonatal seizures.[18] Other clonic or tonic seizure types are possible but are seen less commonly. The myoclonic seizure type can be easily perceived as representing a Moro reflex and can be of a benign origin or indicate a more ominous sign of significant brain damage.[16,18] Additionally, alterations in vital signs (eg, hypertension, tachycardia) of an unclear cause can also represent neonatal seizures.[19]

Although the presentations of neonatal seizures may be subtle, the cause is often associated with significant morbidity and mortality. Ninety percent of seizures in full-term newborns are caused by an identifiable cause.[20] The immature nervous system of neonates not only leads to a restricted repertoire from which patients can demonstrate illness to their families and physicians but also makes it more susceptible to having seizures because of any perturbation in its physiology. This circumstance leads to a broad differential diagnosis list for neonatal seizures. From an emergency medicine standpoint, one substantial cause to consider is infection. There should be a low threshold to initiate the workup of possible meningoencephalitis in neonates who are presenting with seizures. The commonly considered organisms (group B streptococci, *Escherichia coli*, and *Listeria*) may be the culprits; but other entities must also be considered, whether newly acquired or congenital, like toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus.[16]

Fortunately, although infection is extremely important to consider on the differential of neonatal seizures, it is not the most common cause. Hypoxic-ischemic encephalopathy (HIE) is the most common cause of neonatal seizures and usually manifests within the first 48 hours of life.[18] Intracranial hemorrhage should be considered also because it accounts for 10% of neonatal seizures.[16] Birth trauma can lead to subarachnoid or subdural hemorrhage and, because of the subtle nature of the neonatal seizures, may not be noticed until after hospital discharge. Premature infants are particularly at risk for intracranial hemorrhage, and all children are at risk for sustaining injury caused by nonaccidental trauma. Aside from hemorrhage, congenital intracranial anomalies, such as tuberous sclerosis, pachygyria, or lissencephaly, can also lead to seizures in neonates.[19]

Although intracranial abnormalities is intuitively linked to seizures, there are other important entities to consider in neonates who are seizing. Metabolic disturbances and derangements should be considered in neonates with seizures. Hypoglycemia, hypocalcemia, hypomagnesemia, hypernatremia, and hyponatremia are all known to cause seizures and can result from a variety of conditions, from errors in mixing formula to inborn errors of metabolism.[16] Although the indiscriminant investigation of electrolytes is often unnecessary in older patients, chemistry panels can prove to be useful in this at-risk neonatal population,[21] particularly in those who are actively seizing. Seizures caused by inborn errors of metabolism are poorly responsive to conventional therapies for seizures.[20] The specific inborn errors of metabolism that can lead to neonatal seizures are beyond the scope of this review but do warrant consideration as a whole when evaluating a child with neonatal seizures because additional blood, cerebrospinal fluid (CSF), and urine should ideally be obtained and held to assist with making the definitive diagnosis during the hospitalization.

The evaluation and management of neonates with seizures should initially focus on the life-threatening and treatable causes while keeping a perspective about what is common as well as rare. A thorough history and physical examination may help direct the evaluation (eg, fevers, bulging fontanelle, dysmorphic features, hepatosplenomegaly, bruising), but a normal examination does not eliminate the need for concern. After airway, breathing, and circulation issues have been addressed, obtaining a glucose level is imperative. Although infection is not the most common cause of neonatal seizures, the authors think that its potential existence should be addressed rapidly and appropriate cultures obtained and antimicrobials initiated. Metabolic laboratory investigation is also warranted, and the consideration of possible inborn errors of metabolism before the initiation of therapies can aid in making the diagnosis. Emergent neurologic imaging should also be considered to investigate for intracranial pathologies like hemorrhage or congenital anomalies. In neonates, although ultrasound may provide valuable information regarding interventricular or parenchymal hemorrhage, computed tomography (CT) imaging is superior in identifying the extent of intracranial hemorrhage, cortical lesions, subarachnoid blood, and other pathologies and is generally viewed as the preferred imaging modality.[18,22] If patients are clinically stable and there is rapid availability, however, magnetic resonance imaging (MRI) will typically reveal even more detailed and useful information.[23]

Therapeutic medication options for actively seizing neonates still start with benzodiazepines; however, should seizures persist beyond benzodiazepine therapy, phenobarbital is generally favored over phenytoin in neonates.[16,24] Weight-based doses for these medicines are the same as for older children (**Table 1**). Obvious electrolyte abnormalities, such as hyponatremia, should also be promptly corrected. For status epilepticus that is resistant to traditional therapies, pyridoxine dependency may be the culprit, and empiric pyridoxine administration of 50 to 100 mg intravenously may prove to be useful.[16,19]

FEBRILE SEIZURES

Febrile seizures represent an entity unique to pediatric populations that requires special discussion. They are estimated to occur in approximately 2% to 5% of the US pediatric population, with a peak incidence at 18 months.[25] Given the dramatic presentation, often in a previously well child, these patients are almost universally brought to the emergency department for evaluation; thus, it is critical that every

Table 1
Medications to treat status epilepticus

First-Line Medications: Benzodiazepines	
Lorazepam	IV/IM 0.05–0.1 mg/kg (max: 4 mg per dose)
Diazepam	IV 0.2–0.3 mg/kg (max: 10 mg per dose)
	PR 0.5–1.0 mg/kg
Midazolam	IV 0.05–0.1 mg/kg (max: 6 mg per dose less than 6 y; 10 mg per dose 6 y and older)
	IM 0.1–0.2 mg/kg (max: 5 mg per dose)
	IN 0.2–0.3 mg/kg (max: 7.5 mg per dose)
	Buccal 0.15–0.3 mg/kg (max: 20 mg per dose)
Second-Line Medications	
Phenytoin	IV 15–20 mg/kg (no faster than 1 mg/kg/min)
Fosphenytoin	IV/IM 15–20 PE/kg (no faster than 3 PE/kg/min)
Phenobarbital	IV 15–20 mg/kg (no faster than 1 mg/kg/min)
Valproate	IV 20–40 mg/kg load; can follow with 3–6 mg/kg/min infusion
Levetiracetam	IV 20–30 mg/kg load
Dextrose	IV 2–4 mL/kg of 25% dextrose
Pyridoxine	IV 50–100 mg per dose
Infusions for Refractory Status Epilepticus	
Midazolam	IV 0.1–0.3 mg/kg load followed by 0.05–0.4 mg/kg/h
Propofol	IV 2.0–3.5 mg/kg load followed by 125–300 μg/kg/min
Pentobarbital	IV 0.5–1.0 mg/kg load followed by 1–6 mg/kg/h
Ketamine	IV 1–2 mg/kg load followed by 5–20 μg/kg/min
Lidocaine	IV 1–2 mg/kg load followed by 4–6 mg/kg/h

Abbreviations: IM, intramuscular; IN, intranasal; IV, intravenous; max, maximum; PE, phenytoin equivalents; PR, rectally.
Data from Refs.[10,22,111,138]

practicing emergency medicine physician be well versed in the diagnosis, evaluation, management, and anticipated outcomes in this condition.

The generally accepted definition of febrile seizures in the United States set forth by the American Academy of Pediatrics (AAP) "is a seizure accompanied by a fever (temperature ≥100.4°F or 38°C by any method), without central nervous system infection, that occurs in infants and children 6 through 60 months of age."[26] Febrile seizures are further defined as either simple or complex; this classification helps better delineate workup and outcomes. Simple febrile seizures consist of primary generalized tonic-clonic seizures lasting for less than 15 minutes. The postictal period is generally brief, often resolving by the time of evaluation in the emergency department and the child returns to his or her neurologic baseline. Evidence of focality, duration of 15 minutes or more, or recurrence within 24 hours characterize complex febrile seizures (AAP 2011)[27]; about 35% of febrile seizures are thought to be complex and 5% may actually present in febrile status epilepticus.[25] In fact, febrile status epilepticus is thought to account for about one-third of all instances of pediatric status epilepticus cases and is by far the most common cause of status epilepticus in this age group.[1,4]

The exact pathophysiology of febrile seizures remains unclear, with competing theories pertaining to the rate of increase of fever versus the peak temperature. There is also new data suggesting a possible correlation with iron deficiency anemia.[27,28] Evidence does exist that there is a genetic predisposition, with a positive family history

of febrile seizures in about 25% to 40% of patients.[10,25] Additionally, febrile seizures have been associated with specific causes, such as human herpesvirus 6,[29,30] influenza A,[31] and even some routine childhood immunizations.[32–34]

The appropriate management of a child with a febrile seizure focuses on 3 key principles: acute management if the child is still seizing, diagnosis and management of the source of the fever, and anticipatory guidance to parents. It is in the last 2 principles that defining the febrile seizure as simple or complex impacts the care and messages delivered.

As with any seizing patient, acute management of a child with a febrile seizure focuses on the initial management of the airway, breathing, and circulation. Further management of ongoing seizure activity is discussed later; treatment is similar to afebrile seizures, with the addition of antipyretic therapy to control the fever.

From an emergency medicine perspective, the combination of fever and seizure provokes a concern for meningitis. Fortunately, it is known that if the child fits the definition of a simple febrile seizure, then he or she is not at any increased risk for meningitis.[35,36] Comprehensive review of the extensive medical literature on febrile seizures has been used to generate a clinical practice guideline by the AAP.[26] Research, both before and after the release of the newer immunizations for *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, document that the risk of bacteremia, urinary tract infection, and meningitis are similar between children presenting with a simple febrile seizure versus those who present with a fever without seizure.[36–40] Thus, it is recommended that the evaluation of simple febrile seizures essentially become the evaluation of fever alone. Even with aggressive evaluation for a source, approximately 30% of children with a febrile seizure will have no focal illness or specific viral or bacterial cause identified.[38] There is no role or evidence to support routine neuroimaging, specific blood work, or obtaining an electroencephalogram (EEG).[36] It is important, however, to ensure that patients are appropriately diagnosed as having a simple febrile seizure before relying on this information.

While evaluating a child who has presented with a seizure and does fit the definition of simple febrile seizure, often the parental concern will still focus on meningitis. It is important and useful to convey that bacterial meningitis does not typically present with seizure as its sole manifestation.[41] Additionally, in a large study of more than 700 children aged 6 to 18 months with simple febrile seizures, no child had bacterial meningitis.[35] Thus, in the child with a simple febrile seizure, empiric antibiotics are not advantageous and the lumbar puncture is not mandatory. Lumbar puncture is worth consideration if patients are younger than 12 months with a less reliable physical examination, incompletely immunized, or pretreated with antibiotics that might mask the signs and symptoms of meningitis. Certainly, any child with symptoms concerning for meningitis (such as nuchal rigidity, persistent postictal period, altered mental status, or bulging fontanelle) warrants a lumbar puncture for CSF analysis. If CSF is obtained, recent studies suggest pleocytosis should not be attributed to the seizure and instead managed appropriately.[42,43]

In contrast to the well-supported guidelines for the evaluation and management of simple febrile seizure, complex febrile seizures do not have any definitive management guidelines because of the significant clinical heterogeneity within the definition of complex febrile seizures. For example, the febrile 3-year-old child with clear herpangina who has had 2 seizures within a 24-hour period as well as the 18-month-old child who presents with febrile status epilepticus both are classified as complex febrile seizures. Certainly though, these 2 cases represent extremely different clinical scenarios. With each case of complex febrile seizures, a strategy for obtaining laboratory values, cultures, neuroimaging, neurology consultation, and admission needs to be tailored

for the individual based on the available history and physical examination and at the discretion of the treating physicians.

Despite the lack of clear, definitive guidelines for complex febrile seizures, there is some evidence pertaining to the risk of meningitis and the potential benefit of neuro-imaging. In a recent study of more than 500 patients presenting with a complex febrile seizure, 3 patients were ultimately diagnosed with bacterial meningitis; 2 patients had abnormal findings on examination, and 1 patient was presumptively treated for bacterial meningitis based on a lack of CSF but positive blood culture.[44] In the instance of febrile status epilepticus, which is included within the broader category of complex febrile seizures, there is a definite increased risk of meningitis compared with those with simple febrile seizures, with an estimated risk of bacterial meningitis of 12% to 18%.[1,45] Thus, in the case of complex febrile seizures, a lumbar puncture should be strongly considered and any pleocytosis should be appropriately interpreted.

Again, with the complex febrile seizure cohort including a diverse set of conditions, the utility of neuroimaging needs to be addressed on an individual case basis. The child with clinical herpangina and 2 simple febrile seizures in a 24-hour period may not benefit greatly from a CT scan of the brain, whereas the child in febrile status epilepticus may. Routine imaging should not be performed for patients with complex febrile seizures, but rather the clinical scenario should help determine who is at greater risk of having an intracranial abnormality. Abnormalities are generally noted only in patients with an abnormal physical examination.[46,47]

Parental concern surrounding this event will often be appropriately high; thus, it is imperative that for every child who meets criteria for discharge after suffering a febrile seizure, the emergency physician provides appropriate anticipatory guidance to the parents. Guidance should be provided on the risk of recurrence, appropriate precautions in the event of another seizure, subsequent risk of epilepsy, and the generally excellent prognosis for children who suffer febrile seizures despite the lack of therapies to prevent further seizure activity. The risk of recurrence of a febrile seizure is about 33%, with about 10% having multiple seizures.[25] Specific risk factors that increase the risk of recurrence include age less than 18 months, a family history of febrile seizures, a shorter duration of fever before seizing, and lower temperature at onset of seizing. The presence of multiple risk factors increases the likelihood of seizure recurrence further.[25,48,49] Although seizure recurrence is not uncommon, the risk of epilepsy after a child suffers a febrile seizure is the same as the general population at 1%.[50] The risk may increase to 10% in some studies, especially in the context of a pre-existing neurodevelopmental abnormality, family history of epilepsy, patient history of complex febrile seizure, multiple complex features to the seizure, and brief duration of fever.[25,51]

Unfortunately, extensive research on preventing the recurrence of febrile seizures or the subsequent development of epilepsy has been unfruitful. Routine antipyretic therapy during febrile illnesses has not demonstrated any benefit in prevention.[52–54] Intermittent and routine antiepileptic therapy with benzodiazepines, phenytoin, phenobarbital, valproate, and other agents have varying levels of efficacy; however, the range of adverse side effects outweigh any potential benefit.[49,55–57] Fortunately, research also indicates that febrile seizures, even when prolonged, are not associated with any negative impact on cognitive function.[58,59] Thus, the AAP does not recommend routine use of antipyretics or antiepileptics in patients with from febrile seizures.[50] Under extenuating circumstances (eg, febrile status epilepticus, distance from emergency health care, severe parental anxiety), one could consider discharging patients home with a prescription for rectal diazepam for use in case of a prolonged

febrile seizure with appropriate instruction in its use. Fortunately, for most cases of simple febrile seizures, education and reassurance will be all that is required.

NEW-ONSET AFEBRILE SEIZURES

Every year, between 25,000 and 40,000 children in the United States will have an initial afebrile seizure[60]; thus, it is also critical for emergency physicians to understand the basic evaluation of a new-onset afebrile seizure. It is important for one to remember that a seizure does not always equal epilepsy and instead signifies some sort of brain dysfunction that has resulted in abnormal electrical activity in the brain[61]; thus, a broad differential diagnosis beyond epilepsy is required when considering the child who has suffered an afebrile seizure. Naturally, after acute stabilization of patients, a thorough history and physical examination are critical initial steps in the evaluation. A detailed description of the event is critical to categorizing the event as a seizure and further delineation into categories, such as simple, partial, or partial with secondary generalization. A history of focality to the seizure, prior abnormal neurodevelopment, altered fluid intake, recent immigration after years in a developing country, and possible substance exposure or the findings of abnormal skin lesions, hepatosplenomegaly, or retinal hemorrhages all help delineate whether the seizure represents a de novo presentation of epilepsy versus a symptom of another process, such as a brain tumor, hyponatremia, intracranial infection, ingestion, neurocutaneous syndrome (eg, tuberous sclerosis), inborn error of metabolism, or nonaccidental trauma.

Just as the differential diagnosis list for afebrile seizure is diverse, the potential evaluation is vast. There is no standardized laboratory panel for children presenting with an initial afebrile seizure that can be recommended. As documented in the American Academy of Neurology practice parameter on the evaluation of afebrile seizures in children, the yield of routine laboratory studies is abysmally low.[60] Instead, laboratory investigation should be tailored to the individual case as suggested by the patients' history and physical examination. It is prudent to have a low threshold to obtain a bedside glucose because hypoglycemia represents an easily correctable cause of seizure. A basic electrolyte panel may be particularly useful in younger patients because electrolyte abnormalities have been noted more frequently in this population.[21,62] Other studies that may warrant consideration based on the individual patient's history and physical examination include complete blood counts, toxicology screens, ammonia levels, serum organic acids, and urine amino acids. Lumbar puncture may also be considered if there is clinical concern for meningoencephalitis, although the yield of routine CSF studies is extremely low in patients with a normal mental status and physical examination.

Potential structural anomalies and abnormalities also need to be contemplated during the initial evaluation of patients with a new-onset afebrile seizure. There are clear recommendations for neuroimaging in most cases of new-onset afebrile seizures,[63] and emergent CT imaging is available in most emergency departments. However, there is growing concern about the detrimental effects of radiation on the pediatric brain.[64,65] Additionally, it has been found that the information gleaned from the head CT performed after an afebrile seizure seldom results in a change in management or in any acute intervention.[60,66] Studies are also suggestive of the superiority of MRI regarding identifying lesions compared with CT; in one study, 33% of patients with an initially normal CT scan had abnormal findings identified on MRI.[23] Thus, MRI is the preferred modality for definitive neuroimaging.[60,63] Unfortunately, MRI is less readily available on an emergency basis and may require additional resources for sedation in younger patients. Given the risks and benefits of various modalities

of neuroimaging, a uniform approach cannot be recommended. It is thought best to discuss the risks, benefits, and limitations of the imaging modalities against the risk for emergent intracranial pathologic conditions with patients' families and the neurologist on an individual basis.

The desire to obtain the most prudent studies must be balanced with the physician's suspicion for important, emergent pathologic conditions. There are factors that may heighten suspicion for pathologic conditions that might require immediate intervention, such as a stroke or increased intracranial pressure, and, thus, lower the threshold for obtaining emergent neuroimaging (**Box 2**). Unfortunately, the very young (less than 6 months of age) are more difficult to obtain a reliable neurologic examination on; some advocate for obtaining emergent neuroimaging in these patients after a new-onset afebrile seizure.[67] Additionally, a prolonged seizure (>15 minutes), persistent postictal focal deficit, or aberration from neurologic baseline should increase concern for focal disease processes.[60,67] Additionally, patients with a predisposing condition like sickle cell disease, bleeding disorder, cerebrovascular disease, neurocutaneous disorder, malignancy, human immunodeficiency virus, hemihypertrophy, hydrocephalus, travel to an area endemic for cysticercosis, or a closed-head injury should increase suspicion for significant abnormalities.[67,68] Focal seizures in children younger than 33 months should also lower the threshold for obtaining emergent neuroimaging.[68] Otherwise, in the absence of the aforementioned concerning factors, children with a reassuring neurologic examination and an appropriate, established

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Box 2
Factors lower threshold to obtain emergent neuroimaging for first-time afebrile seizure

Findings

- Less than 6 months of age
- Abnormal physical examination
- Prolonged seizure (>15 minutes)
- Persistent postictal period
- Altered mental status
- Persistent focal neurologic deficit
- Focal seizure in child less than 33 months of age
- Closed-head injury
- Travel to endemic area for cysticercosis

Concurrent medical conditions

- Bleeding disorder
- Cerebrovascular disease
- Hemihypertrophy
- Human immunodeficiency virus
- Hydrocephalus/ventriculoperitoneal shunt
- Malignancy
- Neurocutaneous disorder
- Sickle cell disease

Data from Refs.[60,67,68]

outpatient follow-up plan may be appropriate for out-patient MRI rather than CT before discharge from the emergency department.[67]

Before discharge, the family should be informed that the outpatient evaluation would likely also include additionally studies. An EEG is indicated in all children with an afebrile seizure, although the best time to obtain this study remains unclear.[60] Nonspecific abnormalities secondary to the seizure are commonly seen in the few days after a seizure; thus, there is no role for routine EEG before discharge for patients with an initial afebrile seizure who have returned completely to neurologic baseline. However, it is critical that these patients have appropriate outpatient follow-up for EEG within a timely fashion because EEG abnormalities may in fact be the best predictor of seizure recurrence.[69]

Generally speaking, the outcomes of children with a new-onset afebrile seizure are quite good. The overall recurrence rate of seizures is about 54%, with most recurrences occurring within 2 years of the initial seizure; thus, almost half of all children with an initial afebrile seizure will not develop epilepsy. The risk of subsequent epilepsy is increased in patients with an abnormal EEG and history of abnormal neurodevelopment.[70,71] Unfortunately, there are no known therapies that alter a patient's potential progression to epilepsy after an initial afebrile seizure. Because there have been no detrimental effects noted in delaying seizure therapy until after a second seizure, the initiation of antiepileptic medication is not recommended after an initial afebrile seizure, with possible exceptions as discussed earlier in febrile seizures for prescribing rectal diazepam.[72] Antiepileptic medication initiation is best left to the physician who will follow patients long-term and monitor for potential complications. Even among patients who go on to develop epilepsy, outcomes are not completely unfavorable. In one longitudinal cohort of children with epilepsy, around 70% of children were able to achieve remission from seizures and 60% were able to discontinue antiepileptic treatment, whereas only 10% had intractable epilepsy.[73]

STATUS EPILEPTICUS

Most patients who present to the emergency department for evaluation of a seizure are no longer seizing. However, patients who are actively seizing will generate immediate attention; seizure activity may easily recur or develop in any emergency department patient. The annual incidence of pediatric status epilepticus is more than 80,000.[74] This entity accounts for approximately 10% of all patients with new-onset pediatric seizures presenting to the emergency department[4] and is most common in children less than 2 years of age.[75,76] Although there are many potential precipitants of status epilepticus ranging from central nervous system infection to trauma to congenital anomalies to toxins, febrile seizures are the most common cause of status epilepticus in children, accounting for approximately one-third of all episodes[1,77,78]; this is in contrast to adults whereby cerebrovascular accidents represent the most common cause of status epilepticus.[79] Fortunately, the quoted mortality rate for pediatric status epilepticus is quite low, ranging from 3% to 5%.[80,81]

Historically, status epilepticus has been defined as continuous seizure activity for 30 minutes or 2 or more seizures occurring without full recovery of consciousness between episodes.[77] However, there has been a recent trend to categorize seizures lasting longer than 5 to 10 minutes as status epilepticus because there is evidence that seizures are less likely to spontaneously cease after this time frame.[82] From an emergency medicine perspective, the categorization is less vital because it is the patients' clinical condition that mandates the management of the patients.

Although the exact categorical label may still be debated, resolving the seizures as expeditiously as possible is beneficial. With short-duration seizures, the increased metabolic demands of the brain are met with increased cerebral blood flow; however, as the seizure continues, autoregulation can fail and the blood flow to tenuous areas can be compromised, potentially leading to irreversible cerebral damage.[77] Persistent neuronal excitation may also mediate neuronal injury.[83] Furthermore, prolonged seizures can be associated with hyperthermia, myoglobinuria, hyperuricemia, renal impairment, multiple metabolic derangements, aspiration, respiratory failure, hepatic failure, and persistent neurodevelopmental abnormalities.[77,84,85] Finally, there is excellent evidence suggesting that seizures become more refractory to therapy the longer they persist.[75,86,87] In an effort to minimize the chance that the seizure will progress to a refractory state, aggressive therapy should be initiated as soon as possible.

As with all efforts to stabilize patients during emergent conditions, the initial steps should focus on maintaining a patent airway, ensuring there is adequate ventilation, and assessing patients for appropriate circulation. Actively seizing patients can have derangements in one or all of these important systems. Although more aggressive maneuvers may be necessary, often a simple jaw thrust will be adequate to help maintain a patent airway. Supplemental oxygen is advisable if respirations become compromised, and suctioning should be readied in case of emesis. The use of bite blocks to protect the tongue has fallen out of favor given the risk of aspiration.

Although it is reasonable to observe patients briefly before administering medicines in case the seizure spontaneously ceases, there is good evidence that seizures that persist beyond 5 minutes are unlikely to stop[82]; thus, at this point, it is beneficial to administer medications to halt the seizure. Benzodiazepines are considered first line therapy for essentially all seizure disorders; they work by modulating the gamma-aminobutyric acid (GABA) receptor.[88] All medicines in this class carry the risk of respiratory depression and hypotension, necessitating close monitoring for these complications, especially when multiple doses or other medications are given. Each benzodiazepine has unique characteristics and dosing (see **Table 1**). Diazepam is commonly used given its rapid onset secondary to its highly lipophilic properties enabling rapid penetration across the blood-brain barrier. It is also frequently prescribed to patients with known seizure disorders for home administration rectally; it can also be used in this manner in the emergency department if intravenous access has not been established.[89] More recently, midazolam has started to gain favor in the prehospital and emergency department environments because of its ease of use and efficacy via intranasal, intramuscular, and buccal routes.[90–99] Because vascular access is often difficult in pediatric patients (particularly ones who are ill), intramuscular, intranasal, or buccal routes should be considered early in the management. However, when intravenous access is established, lorazepam is the most commonly used benzodiazepine because of its efficacy and duration of action of 6 to 12 hours.[77]

Continued seizure activity despite successive doses of benzodiazepine should lead to the administration of medications that work by a different mechanism (see **Table 1**). Phenytoin and fosphenytoin have traditionally been selected as second-line agents and affect voltage-gated sodium channels. Unfortunately, phenytoin cannot be administered rapidly because of the associated hypotension, widening of the QT interval, and dysrhythmias owing to its diluents. There is also the risk of purple glove syndrome.[77,100,101] Unlike phenytoin, fosphenytoin can be administered more rapidly, safely, and even given intramuscularly; however, it is a prodrug of phenytoin and takes longer to have an effect.[77,102]

Phenobarbital has long held position as a third-line medication in the treatment of status epilepticus. Although it also works on GABA receptors, it does so via a different mechanism from benzodiazepines. It takes longer to terminate seizure activity but has a prolonged therapeutic effect. Although there is no definitive evidence, it is a commonly held belief that phenobarbital is more strongly associated with respiratory depression, potential need for intubation, and hypotension compared with phenytoin. Interestingly, phenobarbital is commonly favored over benzodiazepines as a first-line or second-line therapy for the treatment of neonatal seizures and should be potentially considered for use earlier when managing younger patients.[24,103]

Newer medications have recently demonstrated promise and potential value in the acute management of status epilepticus. Valproate has shown benefit as a second-line medication, with particular utility in patients already maintained on this medication or who have nonconvulsive or partial status epilepticus.[104–110] It also lacks adverse effects on the cardiovascular or respiratory systems but does have potential risks of hepatic dysfunction, parkinsonism, pancreatitis, and thrombocytopenia.[102,111] Levetiracetam has been shown to be safe in children as young as 6 months of age; it is generally well tolerated, and side effects are reversible with cessation of the medication.[112] Levetiracetam also offers the advantage of being able to be converted easily over to oral medications later in the patients' management. Preliminary evidence suggests that levetiracetam may be safely administered intravenously as therapy for status epilepticus, although further research is necessary to recommend routine use of this medication.[110,113–115]

Unfortunately, refractory status epilepticus occurs in 25% of patients with status epilepticus.[116] If patients have continued to seize despite the previous interventions, the seizure is considered to be refractory[117] and patients are at an increased risk for adverse events. Before this period, patients may or may not have required intubation to protect airway patency; however, the management of refractory status epilepticus will require intubation because most therapies will essentially induce general anesthesia and coma. In this scenario, emergent EEG monitoring is of vital importance to guide further therapy because paralytics will mask potential continued convulsions. There are no clear guidelines on what is the most advantageous therapy, but standard options include continuous infusions of midazolam, propofol, pentobarbital, ketamine, and lidocaine. Additional therapies that have growing evidence and may eventually have a standardized role in the management of status epilepticus include lacosamide, magnesium, topiramate, isoflurane, steroids, therapeutic hypothermia, electroconvulsive therapy, vagal nerve stimulation, and emergent surgery.[116,118–122]

Any discussion of status epilepticus would be incomplete without the consideration of nonconvulsive status epilepticus. This entity is thought to account for approximately 25% of all cases of status epilepticus and is more common in patients with certain epilepsy syndromes.[123] The classic subtypes include absence status epilepticus and complex partial status epilepticus. About a quarter of cases of nonconvulsive status epilepticus follow convulsive status epilepticus and represent burnt out or subtle generalized status epilepticus.[123,124] These patients may have a range of altered mental status ranging from mild confusion to psychosis to coma with subtle physical movements, such as twitches or automatisms.[124] Nonconvulsive status epilepticus should be considered in patients with an inexplicable, sudden change in mental status or behavior, clinical concern for encephalopathy, unexplained coma, or delayed recovery of mental status after a seizure.[123–125] EEG monitoring is paramount to be able to make the appropriate diagnosis and management of this entity. Treatment is the same as for convulsive status epilepticus with the possible consideration of valproate as a second-line medication.[124]

ADDITIONAL PEDIATRIC SEIZURE SYNDROMES AND UNIQUE THERAPIES

Although the authors have already discussed febrile seizures, which constitute the largest category of seizures unique to the pediatric population, there are many other seizure syndromes unique to pediatric patients. It is useful for the emergency medicine physician to possess a basic knowledge about a few of these particular syndromes. These entities range from benign, self-limited conditions to neurologically devastating diseases and are further discussed in **Table 2**.

Despite the recent advent of new antiepileptic drugs and generally good prognosis for patients with epilepsy, about 10% of children will have intractable epilepsy.[73,126] Poorly controlled seizures are the primary risk factor for sudden unexpected death in epilepsy, increasing the risk of this event from 1 in 1000 to 1 in 150.[2,127–129] In these cases, novel therapies, including implantable devices, specific diets, and surgery, may be required. Rudimentary knowledge of some of these more aggressive therapies is warranted.

The only implantable device currently approved for use in the United States is the vagal nerve stimulator (VNS). This device consists of an implanted device in a sub-cutaneous pocket, either under the clavicle or in abdominal tissue in smaller patients; a microprocessor and battery are attached to the left vagus nerve via leads. The VNS is typically set to deliver a stimulus designed to terminate seizures when a small handheld magnet is held directly over the device for a few seconds; thus, activation of a VNS may be useful in the management of seizures in patients who possess this technology. If mandated, MRI generally can be completed regardless of VNS placement; but this is best coordinated between neurosurgery and radiology. There is a 3% to 5% risk of infection of the VNS, and lead fractures may occur after direct trauma to the neck. Patients may also present with complaints of twitching, coughing, dysphagia, or other sensations secondary to VNS firing. Continual device activation may occur rarely, and taping the magnet over the patients' VNS should turn it off until neurosurgical evaluation can be obtained. Otherwise VNS are generally helpful in reducing seizure frequency by about half in 50% of all patients.[130,131]

Another therapy that patients with intractable epilepsy may use is the ketogenic diet. Essentially a starvation state is used to induce ketosis, generally resulting in up to a 30% to 40% reduction in seizures in numerous types of epilepsies, with even better results in some individual patients.[132] Within a few weeks of initiation, patients may present with complications, such as dehydration, hypoglycemia, and other metabolic derangements. However, long-term complications are typically limited to osteopenia, nephrolithiasis, and cardiomyopathy. Occasionally, these patients will present to the emergency department with ongoing seizure activity, potentially with hypoglycemia. In this situation, correcting hypoglycemia may actually be harmful and worsen seizure activity by breaking the patients' ketotic state. Thus, dextrose infusion must be reserved for patients with severe hypoglycemia, and other typical seizure therapies should be maximized. Additionally, in cases of refractory status epilepticus, it may be wise to avoid propofol because these patients are at a higher risk of propofol infusion syndrome.[22,133,134]

Occasionally, patients will have seizures of such severity that they may require experimental therapies or even surgery. At present, there are numerous devices,[135] medications, alternative diets, and other therapies under investigation. Surgeries may be particularly beneficial in focal epilepsies and the most intractable diseases. These surgeries, such as hemispherectomy, corpus callosotomy, and anterior temporal lobe resection, may be associated with delayed complications, such as bleeding, hematoma formation, and obstructive hydrocephalus[136]; however, they

Table 2
Seizure syndromes unique to pediatric patients

Benign Convulsions Associated with Gastroenteritis	6–60 mo Peaks 13–24 mo	Afebrile, brief, generalized seizures accompanying symptoms of gastroenteritis without metabolic derangement, fever, or *Shigella* infection; associated strongly with rotavirus, although seen with other viral causes; seizures may cluster, be difficult to treat; spontaneously remits at conclusion of illness[139–141]
Benign Familial Neonatal Convulsions	Initial days of life Remits within 1 y	Presentation may include behavioral arrest, eye deviation, tonic stiffening, myoclonic jerks; associated with positive family history; some may develop subsequent epilepsy[16]
Benign Idiopathic Neonatal Convulsions	Initial days of life Remits within 15 d	Also called "fifth day fits"; presentation may include clonic movements, apnea; associated with positive family history; may account for up to 5% of all seizures in term infants[16]
Absence Seizures	5–10 y Remits by 14 y	Associated with sudden cessation of activity, possible eye fluttering, brief duration (about 30 s), and no postictal period; seizures may be triggered by hyperventilation; 70% of patients spontaneously remit; 40% of patients may have associated generalized tonic-clonic seizures[22,142]
Benign Rolandic Epilepsy	3–13 y Remits by early adulthood	Typically associated with nighttime clonus (especially facial) while sleeping, which may secondarily generalize; associated with autosomal dominant inheritance[22,143]
Juvenile Myoclonic Epilepsy of Janz	12–15 y	Typically associated with myoclonic jerks on awaking, although also many have generalized tonic-clonic or absence seizures; triggered by stress, lack of sleep, alcohol; associated with autosomal dominant inheritance; generally requires ongoing treatment[22,143]
Infantile Spasms	4–18 mo Peaks 4–6 mo	Sudden jerking of extremities, head, neck, and trunk, occasionally with associated cry, typically occurring in clusters; associated with other neurologic conditions (such as tuberous sclerosis, HIE, congenital infections); 95% of patients also have mental retardation; treated with steroids, vigabatrin; spasms typically spontaneously remit, but most patients develop new seizures[143–145]
Lennox-Gastaut Syndrome	3–5 y	Patients suffer from multiple seizure types including tonic, absence, atonic, myoclonic, and status epilepticus; associated with static encephalopathy, mental retardation, intractability despite multiple medications or use of rare therapies, such as surgery, special diets[22,145]

Data from Refs.[16,22,139–145]

may ultimately be the most effective measure in providing relief to patients with intractable epilepsy.[137]

SUMMARY

Pediatric seizures are common and have many characteristics that distinguish them from seizures in adults. Appropriate diagnosis of seizures may be challenging given numerous seizure mimics and the subtle presentation of neonatal seizures. Making an appropriate diagnosis as to the presence of a seizure and any potential cause is critical to delivering appropriate care. Although some entities may be relatively benign, such as febrile seizures, status epilepticus and refractory seizure syndromes can produce significant morbidity and mortality. Fortunately, the outcomes of seizures in pediatric patients are generally excellent; there has been ongoing development of additional therapies, including medications, diets, devices, and surgeries.

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