Febrile seizures are the most common form of childhood seizures, occurring in 2 to 5% of the population. In 1993, the International League Against Epilepsy (ILAE) defined a febrile seizure as a “seizure occurring in childhood after the age of 1 month, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other symptomatic seizures,” including those secondary to acute electrolyte imbalance. This is similar to the definition adopted by the National Institutes of Health Consensus Conference in 1980, except that the lower age limit was shifted from 3 months to 1 month. It is generally accepted that the febrile illness must include a temperature of at least 38.4°C, though not necessarily at the time of the seizure.

Simple febrile seizures are relatively brief (< 10 to 15 minutes) generalized seizures that do not recur during the same febrile illness. Complex febrile seizures are characterized by one of the following features: prolonged duration (> 10 to 15 minutes), partial onset, or multiple recurrences within 24 hours. If a careful history is taken, approximately one-third of all febrile seizures presenting to the emergency room have complex features. Seizures in the context of a febrile illness occurring in a neurologically abnormal child are still considered simple or complex according to the above criteria. Although children who have preexisting neurologic abnormalities are more likely to present with complex febrile seizures and are more likely to develop subsequent epilepsy, they can still have simple febrile seizures.

If the febrile seizure lasts longer than 30 minutes (whether as a single seizure or as a series of seizures) without full recovery between seizures, it is classified as febrile status epilepticus. Febrile status epilepticus accounts for approximately 5% of all febrile seizures. However, because of the frequency with which febrile seizures occur, it accounts for approximately one-quarter of all cases of status epilepticus in childhood and for two-thirds of cases of status epilepticus in the second year of life.

Epidemiology

The U.S. National Collaborative Perinatal Project (NCPP) tracked 54,000 children and determined the prevalence of febrile seizures at 7 years of age to be 3.5% in Caucasian children and 4.2% in African American children. Studies in Western Europe reported a similar prevalence. Febrile seizures occur more frequently in Japanese children, 9 to 10% of whom experience at least one episode, which may indicate a genetic predisposition in this population. The onset of febrile seizures peaks between 18 and 22 months of age, and most cases occur between 6 months and 3 years of age. Onset of febrile seizures after age 5 years is uncommon, but seizures can occur up to 10 years of age. Some studies have reported a slightly higher incidence among boys than girls.

A case-controlled, population-based study identified the risk factors associated with first febrile seizure as follows:

- History of febrile seizures in a first- or second-degree relative
Children with two of these risk factors have an almost 30% chance of developing febrile seizures. A case-controlled study to identify which children with a febrile illness were likely to develop seizures found that family history of febrile seizures and peak temperature were important risk factors. The specific type of illness also was relevant. Children with gastroenteritis and fever were less likely to have a febrile seizure than were children with other types of febrile illnesses.

In the past, febrile seizures were thought to usually occur as the first sign of a febrile illness. A study by Berg and colleagues in 1997 found that only 21% of children experienced febrile seizures before or within an hour of recognized fever onset. Most (57%) had a seizure after 1 to 24 hours of recognized fever, and 22% had seizures more than 24 hours after the onset of fever.

**Initial Evaluation**

To make the diagnosis of febrile seizures, meningitis, encephalitis, accidental poisoning, trauma or abuse, electrolyte imbalances, and other causes of acute symptomatic seizures must be excluded. Of these, the one of most concern to the clinician is meningitis. The incidence of meningitis in children with first seizures associated with fever is 2 to 5%. The following risk factors for meningitis have been identified:

- A visit for medical care within the previous 48 hours
- Focal or prolonged seizures
- Suspicious findings on physical or neurologic examination

The American Academy of Pediatrics (AAP) has issued guidelines for evaluating children aged 6 months to 5 years who have simple febrile seizures. A spinal tap should be strongly considered in an infant less than 12 months of age. Because signs of meningitis may be subtle in the 12- to 18-month age group, careful assessment is mandatory. A spinal tap is not necessary in a child older than 18 months if the history and physical examination are not suspicious for meningitis. A spinal tap is still recommended in children with first complex febrile seizures or with any other risk factors listed, as well as in those with persistent lethargy or prior antibiotic therapy.

Many studies have found that in the absence of suspicious history (eg, vomiting or diarrhea) or abnormal physical examination findings, routine measurement of serum electrolytes, calcium, phosphorus, magnesium, complete blood count, and serum glucose is of limited value in the evaluation of a child with febrile seizures who is older than 6 months. In younger children, more detailed laboratory investigations may be helpful in select cases.

Neuroimaging studies are not helpful in the evaluation of simple febrile seizures. The role of neuroimaging in the evaluation of complex febrile seizures is more controversial. Neuroimaging may be useful in evaluating a child with a prolonged focal seizure, particularly when the etiology of the seizure is not clear. Magnetic resonance imaging (MRI) may be of use in assessing whether hippocampal damage has occurred after febrile status epilepticus, though the clinical utility of this finding is not yet fully established. Data show that prolonged febrile seizures can result in acute hippocampal injury and subsequent mesial temporal sclerosis, but imaging cannot be used to predict who will develop intractable temporal lobe epilepsy. Other studies have shown that MRI abnormalities in the hippocampus after febrile status epilepticus may be transient and, therefore, not detected, unless the study is performed shortly after the prolonged seizure occurs.

Electroencephalogram (EEG) is of limited value in evaluating a child with febrile seizures. The clinical relevance of EEG abnormalities in this setting is unclear, because they do not predict febrile seizure recurrence or development of epilepsy. Evidence does not support the previously held belief that performing an EEG 2 weeks after the febrile seizure helps distinguish benign febrile seizures from other types.

**Pathophysiology**

The pathophysiology of febrile seizure remains elusive. It is clearly an age-specific phenomenon. Animal models of febrile seizures demonstrate an age-specific susceptibility to seizures induced by fever. Induction of epileptiform activity by temperature elevation has been demonstrated in hippocampal slices of rat pups. In animal models, febrile seizures begin in the hippocampus or amygdala. There is little evidence of neuronal death in the normal immature rat, even after very prolonged febrile seizures. More recently, long-term functional changes in the hippocampal circuit after febrile seizures lasting 20 minutes have been described in a rat model. However, whether these changes lead to epilepsy remains unclear. Interestingly, seizures lasting less than 10 minutes are not associated with any anatomic or functional changes. Young rats with induced neuronal migration disorders are more susceptible to seizures induced by fever as well as to hippocampal damage. These results suggest that preexisting central nervous system (CNS) anomalies may make the brain more susceptible to prolonged seizures and to seizure-induced injury.

Clinically, febrile seizures are associated with febrile illnesses but do not necessarily occur at the peak temperature or on the rising phase of the fever. The most commonly
associated illnesses are upper respiratory infections, otitis media, and herpesvirus infections, including roseola. Up to 50% of febrile seizures in children younger than 3 are associated with human herpesvirus (HHV 6 and 7) infections. Whether this occurs because these viruses are neurotropic or because these infections are typically associated with high fevers remains unclear. Of note, gastroenteritis seems to protect against febrile seizures, with the notable exception of Shigella infection.

**Morbidity and Mortality**

The morbidity and mortality associated with febrile seizures is extremely low, even in the case of febrile status epilepticus. No deaths were reported from the NCPP or the British Cohort Study. No deaths and no cases of new motor or cognitive impairment occurred in a recent series of 180 cases of febrile status epilepticus.

Cognitive and behavioral outcomes after febrile seizures also are favorable. The NCPP found no difference in intelligence quotient (IQ) scores or performance on the Wide Range Achievement Test between children with febrile seizures and their siblings. Similarly, the British Cohort study found no differences in measure of IQ, academic achievement, or behavior between children with febrile seizures and children without febrile seizures in the same birth cohort. The favorable cognitive and behavioral outcomes in these two large, well-designed prospective studies apply to children with both simple and complex febrile seizures, including febrile status epilepticus.

**Recurrent Febrile Seizures**

Approximately one-third of children who have a febrile seizure will have at least one recurrence. Multiple studies have identified the following as the most consistent risk factors for recurrent febrile seizures:

- Family history of febrile seizures
- First febrile seizure before age 18 months
- Temperature (the lower the fever, the higher the risk of recurrence)
- Brief duration (< 1 hour) between onset of recognized fever and seizure

Children with two or more risk factors have a 30% recurrence risk at 2 years; those with three or more risk factors have a 60% recurrence rate. One-half of all recurrences are within the first 6 months, and 90% occur within 2 years. A complex febrile seizure is not associated with an increased risk of recurrence in most studies. However, complex features tend to persist if recurrences occur. In particular, children who have a prolonged initial febrile seizure and have a recurrence are likely to have a prolonged recurrent seizure as well.

**Febrile Seizures and Subsequent Epilepsy**

Data from large epidemiologic and prospective studies indicate that 2 to 10% of children with febrile seizures will develop epilepsy. In most studies, the risk of developing epilepsy after a single febrile seizure is not substantially different than that of the general population. Even in populations with a high incidence of febrile seizures, such as the Japanese, the incidence of epilepsy is not significantly different from that in populations with a lower incidence. The pessimistic view that febrile seizures cause brain damage, which prevailed in the older literature, was based on a select population and has been refuted by prospective studies.

Risk factors for epilepsy after febrile seizures are as follows:

- Preexisting neurodevelopmental abnormality
- Complex febrile seizures
- Family history of epilepsy
- Short duration of recognized fever before seizure

Note that contrary to prior views, a short duration of recognized fever prior to seizure onset is not only associated with higher risk of subsequent febrile seizures, but also with increased risk for subsequent epilepsy. This is the only risk factor that recurrent febrile seizures and subsequent epilepsy share. In the case of complex febrile seizures, multiple complex features may be additive and may increase the risk. Children with prolonged and focal febrile seizures are particularly at high risk for developing subsequent epilepsy. Two of the most important risk factors for epilepsy are neurodevelopmental abnormality and a family history of epilepsy, whether or not there is a history of febrile seizures. Family history of febrile seizures, age at first febrile seizure, temperature, gender, and ethnicity have not been shown to increase the risk for developing subsequent epilepsy.

**Do Febrile Seizures Cause Mesial Temporal Sclerosis?**

Retrospective clinical studies from epilepsy surgery centers, where many patients with mesial temporal sclerosis had a history of focal or prolonged febrile seizures, have suggested a causal relationship between prolonged febrile seizures and subsequent temporal lobe epilepsy. However, large population-based studies and prospective studies have failed to find this association. Recent imaging data suggest that very prolonged febrile seizures lasting more than 60 minutes may cause hippocampal damage, particularly in brains that already have some preexisting abnormalities. This is so rare that even large prospective series may not have enough cases to detect its occurrence. The frequency with which this occurs remains an unanswered question.
Genetics

Genetic factors clearly play a role in febrile seizures but are not the whole story. Children with a family history of seizures are at increased risk for both febrile seizures and recurrent febrile seizures. However, it would appear that given the appropriate febrile illness in the age-specific period of vulnerability, most children would be at risk for febrile seizures. What proportion of the risk is attributable to genetic causes is somewhat unclear. Studies have shown a concordance rate of 56% in monozygotic twins and 14% in dizygotic twins. Analysis of the Rochester, Minnesota registry points to a multifactorial mode of inheritance for febrile seizures. Recently, a generalized epilepsy with febrile seizures plus syndrome (GEFS+) has been described in families in whom seizures are inherited in an autosomal-dominant pattern, with high penetrance. Affected children tend to have febrile seizures that persist beyond the expected age and may develop generalized tonic-clonic seizures in adolescence (with eventual remission). One-third of abnormal gene carriers have other epileptic syndromes, including absence, myoclonus, and akinetic seizures. The gene codes for a neuronal voltage-gated sodium channel and at least three different mutations have been described so far. The role of specific genetic mutations in febrile seizures is a rapidly evolving field and it will take at least a few more years before sufficient data become available to be of practical use to the pediatrician.

Available Treatment Modalities

Antipyretic Agents

As febrile seizures, by definition, occur in the context of febrile illness, one would assume that aggressive treatment with antipyretic medication would reduce the risk of febrile seizure. However, controlled clinical trials provide little evidence to suggest antipyretics reduce the risk of recurrent febrile seizure. It should be noted that children in whom febrile seizures occur at the onset of fever have the highest risk of recurrent febrile seizures. Recommendations for antipyretic therapy should recognize its limitations and avoid creating feelings of undue anxiety and guilt in parents.

Continuous Anticonvulsant Therapy

Phenobarbital given in doses that achieve serum levels of 15 µg/mL or sodium valproate effectively reduce recurrence risk. However, the morbidity of therapy, including cognitive and behavioral side effects in the case of phenobarbital and the potential for hepatic failure in young children treated with valproate, is such that this therapy is indicated only in rare cases. Even for children with recurrent febrile status epilepticus, or multiple episodes of complex febrile seizures, daily therapy is rarely recommended. Instead, these children are treated with oral diazepam when febrile to reduce their risk for seizure recurrence. Additional treatment includes abortive therapy with rectal diazepam at the time of seizure.

Carbamazepine and phenytoin have not been shown to effectively prevent simple febrile seizure recurrence. There are insufficient data on the newer antiepileptic drugs, including gabapentin, lamotrigine, topiramate, tiagabine, and vigabatrin, to justify their use in the treatment of febrile seizures.

Intermittent Antiepileptic Drug Therapy

Diazepam, given orally or rectally at the onset of illness, can reduce the risk of recurrent febrile seizures by up to 44%. Sedation is the most significant adverse effect. Drawbacks are the number of times therapy may be needed, considering the frequency of febrile illnesses in early childhood. There is also the theoretical concern that sedation could mask signs of a more serious illness, such as meningitis. There is less experience with other benzodiazepines, though presumably some of them would be effective.

Intermittent therapy with phenobarbital at the onset of a febrile episode has been shown to be ineffective in reducing the risk of seizure recurrence, most likely because of the long time needed to achieve meaningful serum levels. Intermittent therapy with valproate is also ineffective.

Intermittent Benzodiazepines for Stopping a Febrile Seizure Episode

Interrupting a prolonged seizure is desirable. Most febrile seizures are brief, lasting less than 10 minutes, and no intervention is necessary. Rectal diazepam has been shown to be effective in terminating febrile seizures. It is widely used in Europe, Canada, and Japan, and increasingly in the United States. It would seem a rational therapy for abortive therapy when needed. Candidates for this treatment include children at high risk for prolonged or multiple febrile seizures and those who live far from medical care. This approach has the obvious advantage of minimizing drug exposure. However, it should be used only with reliable caregivers who have been trained in its use. Other benzodiazepines also have been used, including rectal lorazepam and buccal midazolam, though there is far less experience with them than with rectal diazepam.

Emergency Department Treatment of Febrile Seizures

A child who arrives in the emergency department seizing should be treated using the department’s pediatric status epilepticus protocol. Usually this calls for intravenous benzodiazepines, either diazepam or lorazepam. If no intravenous access is available, rectal diazepam can be
used. In general, once a febrile seizure stops, it stops completely, so there is usually no need to load the patient with fosphenytoin. Loading can be done if the child continues to seize. A full discussion of the treatment of status epilepticus is beyond the scope of this chapter and is covered elsewhere in this volume. The child who has a febrile seizure in the emergency department can be treated more conservatively with rectal diazepam if the seizure does not stop within a few minutes, and the full status protocol is not usually needed.

**Treatment of Children with Febrile Seizures**

Treatment of febrile seizures is a controversial subject. There are two major rationales for treatment, each leading to different approaches. The first approach is based on the old idea that febrile seizures are harmful and may lead to the development of epilepsy and is aimed at preventing febrile seizures using either intermittent or chronic treatment with medications. However, several studies have shown that although these therapies reduce the risk of recurrent febrile seizures, they have no effect on the rate of development of subsequent epilepsy. The second approach is based on epidemiologic data that indicate febrile seizures are generally benign. Therefore, the only concern is very prolonged febrile seizures. These considerations lead to a therapeutic approach that focuses on aborting febrile seizures when they occur to prevent status epilepticus.

**Treatment of Simple Febrile Seizures**

The AAP has issued practice guidelines stating that most children with simple febrile seizures do not require treatment. Antipyretics are ineffective and the morbidity of chronic or intermittent antiepileptic drug therapy makes them unsuitable for the treatment of an essentially benign condition, despite their efficacy. We fully agree with this position. In patients who live far from medical care or whose parents or caretakers are particularly concerned, a prescription for rectal diazepam may be appropriate.

**Treatment of Complex Febrile Seizures**

There is no consensus on the treatment of complex febrile seizures. However, few practitioners would recommend chronic prophylactic therapy, except in exceptional cases. Recommended therapies for these patients include intermittent diazepam at the time of fever and rectal diazepam if a seizure should occur and last longer than 5 minutes. We prefer rectal diazepam for the reasons discussed above. If intermittent diazepam is used at time of fever and a seizure does occur, rectal diazepam can still be given as an abortive agent with good safety and efficacy.

**Conclusion**

In summary, febrile seizures are common and mostly benign form of seizure. Daily antiepileptic drugs are not recommended for children with simple febrile seizures and often are unnecessary, even for those with complex febrile seizures. The rationale for treatment is prevention of prolonged or repetitive febrile seizures.

The clinician needs to recognize that seizures are frightening events for those who witness them. Parents need to be reassured that the child will not die during a seizure, a widespread fear. Keeping the child safe during a seizure usually is the only measure needed. Parents should be offered information about febrile seizures, prognosis, and management. If rectal diazepam gel is prescribed, explicit information regarding its correct administration needs to be provided. Proper education about when to contact their clinician for evaluation of the source of fever is key to proper management, even if medications are not prescribed. Understanding the natural history and prognosis of febrile seizures helps the physician counsel families and choose appropriate management, while avoiding unnecessary diagnostic procedures and therapies.

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**Suggested Readings**


Practitioner and Patient Resources

**Epilepsy Foundation**
4351 Garden City Dr., Suite 406
Landover, MD 20785-2267
Phone: (301) 459-3700 or (800) EFA-1000
E-mail: postmaster@efa.org
www.epilepsyfoundation.org

**American Academy of Pediatrics (AAP)**
141 North West Point Boulevard
Elk Grove Village, IL 60007-1098
Phone: (847) 434-4000
Fax: (847) 434-8000
www.aap.org
Practice guidelines on evaluation and treatment, an information fact sheet about febrile seizures (also available directly from AAP), and regularly updated information.

**National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)**
Bethesda, MD 20892-2540
www.ninds.nih.gov