

REVIEW ARTICLE

Pediatrics

Febrile seizures: A review

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Funding and support: By JACEP Open policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Abstract

Febrile seizures are common, occurring in up to 5% of children in the United States. Frequently perceived by caregivers as a life-threatening event, febrile seizures are a common cause of emergency department visits. The concern for permanent neurologic sequelae and future epilepsy after febrile seizures has resulted in a significant amount of research on these topics. The development of childhood vaccines over the past several decades has led to a significant reduction in childhood bacterial meningitis. This in turn has led to a dramatic change in the evaluation and treatment of febrile seizures. In this review, the different types of febrile seizures as well as the evaluation and prognosis of each are discussed.

KEYWORDS

complex febrile seizure, febrile seizure, febrile status epilepticus, simple febrile seizure

1 | INTRODUCTION

Febrile seizures are the most common seizures in children younger than 5 years.¹ They are defined as a seizure accompanied by a fever of at least 100.4°F (38°C) without central nervous system infection, that occurs in children 6 through 60 months of age.² Frequently perceived by parents as a life-threatening event,³ febrile seizures are a common cause of pediatric emergency department visits. In this guided review, we discuss the different classifications of febrile seizures and specifically address their evaluation, treatment, and prognosis. The purpose of this article is to assist practicing emergency physicians who treat these children.

2 | EPIDEMIOLOGY

The incidence of febrile seizures is estimated to be between 2% and 5% in the United States and Western Europe.⁴ Some studies have found a higher incidence of 8%–10% in Asian populations.^{5,6} The peak incidence of a first febrile seizure is in the second year of life, with 90% of children experiencing their first febrile seizure by the age

of 3 years.^{7,8} Febrile seizures occur most frequently in the winter months, concurrently with febrile episodes.⁹ Some studies have found a higher incidence of febrile seizures in males, and others have found no significant difference based on gender.¹⁰

3 | ETIOLOGY

Genetic factors seem to play a role in febrile seizures, with approximately one third to one half of children with febrile seizures having a family history thereof.^{11,12} Viral infections, commonly influenza, adenovirus, parainfluenza, and herpesvirus-6 (roseola infantum), are the pathogens most often responsible for febrile seizures.^{13–15} Otitis media is the most common cause of febrile seizures caused by a bacterial pathogen.¹³ Febrile seizures may occur after the administration of certain vaccines, most commonly those containing measles (measles, mumps, and rubella), combined diphtheria-tetanus toxoids-pertussis, pneumococcal conjugate vaccine (PCV 13), and influenza vaccines.¹⁶ The rapid onset of fever was previously thought to be a precipitating cause of febrile seizures, though this is no longer thought to be true.¹⁷ The height of the fever is the main influencing factor for febrile seizures. Simply put, the higher the temperature, the greater the likelihood of a febrile seizure. One study found the risk of having a febrile

Supervising Editor: Sing-Yi Feng, MD.

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TABLE 1 Clinical characteristics of simple and complex febrile seizures and febrile status epilepticus

Simple	Complex	Febrile status epilepticus
Generalized seizures without focal features	Seizures with focal features	Seizures lasting more than 30 minutes
Less than 15 minutes duration	Seizures lasting more than 15 minutes and those lasting less than 15 minutes stopped with anticonvulsant medication	Brief serial seizures without consciousness being regained during the interictal periods with a total duration of more than 30 minutes
No recurrence within 24 hours	Recurrent seizures within 24 hours	
No preexisting neurologic abnormality	Presence of a preexisting neurologic abnormality Postictal neurologic abnormality, such as Todd's paralysis	

seizure nearly doubled with each increase in degrees Fahrenheit above 101°F.¹⁸

4 | CLINICAL MANIFESTATIONS

Febrile seizures typically occur within the first 24 hours of an illness, often within an hour of fever onset.¹⁹ The seizure is the first sign of a febrile illness in 25%–50% of cases.²⁰ Febrile seizures have an average duration of 4–7 minutes, with only 10%–15% of them lasting longer than 10 minutes.^{21–23} Patients typically have a high fever, with an average of 39.4°C in one study.²²

Signs and symptoms of febrile seizures include loss of consciousness, irregular breathing, pallor or cyanosis, foaming at the mouth, eyes rolling back or fixed gaze, generalized or focal twitching, and jerking of the extremities.²⁴ The facial muscles are often involved.²⁵ Atonic and tonic spells have also been described.²⁵ After the seizure, a postictal period of drowsiness, fussiness, or confusion may occur lasting up to 30 minutes.²⁴ A postictal palsy (Todd's paralysis) may occur.²⁶

5 | CLASSIFICATIONS

Febrile seizures have been classified as simple, complex, and febrile status epilepticus based on duration, the presence of focal features, and recurrence (Table 1).^{2,26} Approximately, 70% of febrile seizures are simple, 25% are complex, and 5% are classified as febrile status epilepticus.^{4,10,27–30} Febrile status epilepticus is the most common cause of status epilepticus in children.³¹

6 | EVALUATION

The evaluation of a child with a febrile seizure should begin with a history and physical examination to determine the cause of the fever. Key features of the history include a description of the seizure and its duration, recent illnesses or antibiotic use, personal or family history of seizures or epilepsy, recent vaccinations, and immunization status for *Haemophilus influenzae* type B and *Streptococcus pneumoniae*.^{2,25,32} Physical examination should search for signs of meningitis such as depressed sensorium, irritability, a bulging fontanelle, nuchal rigidity,

and decreased muscle tone. Unfortunately, in very young children the signs of meningitis may be subtle or not present at all.

6.1 | Laboratory studies

As with any patient presenting with seizure, a serum glucose level should be assessed. Routine laboratory studies in patients with simple febrile seizures are not necessary because electrolyte abnormalities are rare.^{2,33,34} Further laboratory testing in patients should be individualized and guided by history and physical examination findings. The causes of fever in children with and without seizure are similar. Children with simple febrile seizures do not have an increased risk of pneumonia, urinary tract infection, bacteremia, or bacterial meningitis compared to other febrile children.^{35–38}

6.2 | Neuroimaging

No data have been published that either support or negate the need for neuroimaging, specifically computed tomography or magnetic resonance imaging (MRI), in the evaluation of children with simple febrile seizures. The American Academy of Pediatrics (AAP) recommends against the performance of routine neuroimaging in patients with simple febrile seizures.² Similarly, a study of 71 neurologically normal children with a first complex febrile seizure found no significant intracranial pathology that warranted intervention, leading the authors to conclude that neuroimaging is not indicated in this population.³⁹ One study has suggested the value of MRI after febrile status epilepticus to predict future epilepsy.⁴⁰ However, MRI in the evaluation of febrile status epilepticus is not required on an emergency basis.⁴⁰ Although no published guidelines exist specifically addressing this issue, it is probably reasonable to obtain neuroimaging on any febrile seizure patient in whom a postictal neurologic deficit is present.

6.3 | Lumbar puncture

At the forefront of the clinical approach to a child with a febrile seizure is the concern for bacterial meningitis. This concern is well founded because 1 in 4 children with bacterial meningitis will present with a

seizure.⁴¹ Any child presenting with a febrile seizure and signs and symptoms of meningitis should undergo lumbar puncture.

Introduction of the *Haemophilus influenzae* type B and *Streptococcus pneumoniae* vaccines has led to a dramatic reduction in childhood bacterial meningitis.⁴² The most recent AAP guideline on the topic does not recommend the routine performance of a lumbar puncture on all children with a simple febrile seizure.² Rather, the guideline presents lumbar puncture as an option in children between 6 and 12 months of age whose immunization status for *Haemophilus influenzae* type B and *Streptococcus pneumoniae* is incomplete or unknown.² This recommendation was backed by studies in the postvaccine era that demonstrated a near non-existent risk of bacterial meningitis in well-appearing children after a simple febrile seizure.^{35,38,43} The guideline further states that lumbar puncture is an option in those children being treated with antibiotics at the time of the seizure, because antibiotic treatment can mask signs and symptoms of meningitis.²

Traditionally, complex febrile seizures have been cited as a risk factor for bacterial meningitis.^{44,45} Lumbar puncture performed in the evaluation of complex febrile seizure varies by practitioner,⁴⁶ and no national practice guidelines have been established. One recent large study of physician practice patterns when evaluating children with complex febrile seizures found that approximately one quarter of the patients underwent lumbar puncture in the ED.⁴⁷ The authors also noted that the proportion of patients evaluated with lumbar puncture decreased from 31.4% to 17.8% over the course of the 8-year study.⁴⁷ Several studies have documented a very low incidence of bacterial meningitis in otherwise well-appearing children with a complex febrile seizure.^{43,47-50} Two guidelines published in the postvaccine era have suggested performing a lumbar puncture on children with a complex febrile seizure only if they are under 12 months of age.^{51,52} Another recently published guideline suggests performing a lumbar puncture after complex febrile seizure only if the child's clinical examination is suggestive of meningitis.⁵³

Children with febrile status epilepticus are at higher risk for meningitis compared to those with simple and complex febrile seizures. Studies have documented rates of bacterial meningitis of 12% and 17% with febrile status epilepticus.^{54,55} Two recently published guidelines recommend performing a lumbar puncture on all children with febrile status epilepticus.^{25,32} Indications for lumbar puncture after a febrile seizure are listed in Table 2

7 | MANAGEMENT

Most febrile seizures will resolve spontaneously before presentation to the ED. For those that have not resolved, international consensus is that an anticonvulsant drug should be administered for any tonic-clonic seizure that has been ongoing for more than 5 minutes.⁵⁶ Treatment of febrile status epilepticus is the same as for non-febrile status epilepticus. In the United States, rectal diazepam is the most commonly used medication for out of hospital treatment of pediatric seizures.³⁰ A 2018 Cochrane systematic review found that intravenous lorazepam and diazepam have similar rates of seizure cessation with a low risk

TABLE 2 Indications for lumbar puncture after a febrile seizure

- Any child with physical examination findings suggestive of meningitis
- Simple febrile seizures
 - Children between 6 and 12 months old if immunization status is unknown or incomplete
 - Children on antibiotics
- Complex febrile seizures if under 12 months old
- All children with febrile status epilepticus

TABLE 3 Medications used to treat febrile status epilepticus^{25,58}

First-line medications (may repeat dosing after 5 minutes)	Second-line medications
Lorazepam 0.1 mg/kg IV. Maximum dose 4 mg.	Levetiracetam 60 mg/kg IV. Maximum dose 4500 mg.
Diazepam 0.2 mg/kg IV. Maximum dose 10 mg.	Fosphenytoin 20 mg phenytoin equivalents IV. Maximum dose 1500 mg.
If IV access not available:	Valproate 20–40 mg/kg IV.
Midazolam 0.3–0.5 mg/kg buccally, OR 0.2 mg/kg intranasally, OR 0.1–0.2 mg/kg IM. Maximum dose 10 mg.	Phenobarbital 20 mg/kg IV. Maximum dose 1 gram.
Diazepam 0.5 mg/kg buccally, OR 0.2 mg/kg intranasally, OR 0.5 mg/kg rectally. Maximum dose 20 mg.	

Abbreviation: IV, intravenous.

of adverse events.⁵⁶ In the absence of intravenous access, midazolam, given buccally, intranasally, or intramuscularly, or diazepam, given buccally, intranasally, or rectally, are reasonable alternatives.⁵⁶

Febrile status epilepticus rarely stops spontaneously and often requires more than 1 antiepileptic medication.⁵⁷ Repeat doses of benzodiazepines can be administered after 5 minutes. Second-line anti-seizure medications such as levetiracetam, fosphenytoin, valproate, or phenobarbital may be necessary⁵⁸ (Table 3).

8 | PREVENTION

Prevention of febrile seizures with antiseizure medication has been extensively studied. A 2017 Cochrane review found that continuous treatment with phenobarbital and intermittent treatment with diazepam prophylactically was effective at reducing the recurrence of febrile seizures.⁵⁹ However, there were adverse effects in up to 30% of cases, leading the authors to advise against the use of these medications.⁵⁹ Similarly, the AAP advises against the use of continuous and intermittent prophylactic antiseizure medication for febrile seizures.⁶⁰

Because fever is the cause of febrile seizures, it would seem intuitive that antipyretic agents would be of value in preventing recurrence. However, several studies evaluating the value of prophylactic

TABLE 4 Risk factors for recurrence of febrile seizures^{68,71-73}

Age younger than 18 months
Occurrence of the febrile seizure within 1 hour of fever onset
Occurrence of the febrile seizure with a relatively low-grade fever
A history of febrile seizures in a first-degree relative

TABLE 5 Risk factors for epilepsy after a febrile seizure^{68,74-79}

Complex febrile seizure
Occurrence of the febrile seizure within 1 hour of fever onset
Age older than 3 years at the time of the first febrile seizure
Preexisting neurodevelopmental abnormality
Family history of epilepsy

antipyretics given to prevent febrile seizures have failed to support this concept.⁶¹⁻⁶⁵ The AAP has concluded that “although antipyretics may improve the comfort of the child, they will not prevent febrile seizures.”⁶⁰

9 | PROGNOSIS

9.1 | Neurologic sequelae

A key concern among parents of children with febrile seizures is the possibility of long-term neurologic sequelae. In general, population-based studies have not demonstrated an obvious association between simple and complex febrile seizures or status epilepticus and the later development of neurologic or cognitive defects.⁶⁶⁻⁶⁹

9.2 | Risk of recurrence

Recurrence of febrile seizures has been extensively studied. Approximately, one third of children who experience 1 febrile seizure will have another episode during their childhood.⁷⁰ Age at the time of the first febrile seizure appears to be the most important factor for febrile seizure recurrence. One study found a recurrence rate of 50% in patients who were younger than 1 year at the time of the first febrile seizure and a recurrence rate of 20% in patients who were older than 3 years at the time of the first febrile seizure.⁷¹ Other identified risk factors for recurrence of febrile seizures are listed in Table 4.

9.3 | Risk of epilepsy

The risk of future epilepsy after a febrile seizure is dependent on the type of febrile seizure, among other factors (Table 5).^{68,74-79} From 1% to 2% of children with simple febrile seizures will go on to develop epilepsy, compared with approximately 0.5% of children without febrile seizures.^{77,80} Children with complex febrile seizures are at higher risk, with 6%–8% later diagnosed with epilepsy.^{74,80}

10 | INDICATIONS FOR ADMISSION

The majority of children with febrile seizures will not require hospital admission.²⁵ Most can be safely discharged after a period of observation if they have returned to their neurologic baseline. There is no evidence that hospitalization of children after a febrile seizure merely to reassure parents is of any benefit.⁵¹ All children who undergo lumbar puncture in the ED evaluation of a febrile seizure should be admitted.

11 | FUTURE CONSIDERATIONS

Several relatively small studies have evaluated the intermittent and chronic use of the antiseizure medications valproate and levetiracetam, as well as pyridoxine, melatonin, and zinc sulfate to prevent febrile seizures.⁸¹⁻⁸⁶ Although these studies demonstrated some marginal success at febrile seizure prevention, a 2021 Cochrane systematic review concluded there is currently insufficient evidence to support the use of these agents for this purpose.⁸⁷ Clearly, more research is needed in this area.

Recent studies have revealed the role of elevated cytokines in the serum and cerebrospinal fluid with febrile seizures.⁸⁸ Ideally, a therapeutic agent for specific cytokines could be developed to prevent febrile seizures. Also discovered recently was a relationship between iron deficiency anemia and vitamin D deficiency and febrile seizures.⁸⁸⁻⁹¹ Treatment of these deficiencies may play a role in the future prevention of febrile seizures. Finally, a clinical trial funded by the National Institute of Neurological Disorders and Stroke is currently underway evaluating the utility of serum von Willebrand factor and copeptin levels as a biomarker of febrile seizure. This information would be of significant value when trying to discern a febrile seizure from a non-ictal event such as fever with shivering.

12 | CONCLUSIONS

Febrile seizures are the most common type of seizure in preschool-age children and are often perceived as life-threatening events by parents. Introduction of the *Haemophilus influenzae* type B and *Streptococcus pneumoniae* vaccines has dramatically changed the extent of evaluation necessary in children with febrile seizures. Classification of febrile seizures by their duration and other characteristics is key to guide their management and prognosis.

ACKNOWLEDGMENT

This work has not previously been presented. No grants or other financial support was used in the preparation of this manuscript.

CONFLICTS OF INTEREST

We have no conflicts of interest to report.

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How to cite this article: Eilbert W, Chan C. Febrile seizures: A review. *JACEP Open.* 2022;3:e12769.
<https://doi.org/10.1002/emp2.12769>