Evaluation and Management of Simple and Complex Febrile Seizures

A CME Web-Based Monograph

Editor

Shlomo Shinnar, MD, PhD

Professor of Neurology, Pediatrics, and Epidemiology & Population Health

Hyman Climenko Professor of Neuroscience Research

Director, Comprehensive Epilepsy Management Center

Montefiore Medical Center, Albert Einstein College of Medicine

Bronx, New York

UK UNIVERSITY OF KENTUCKY

This activity is jointly sponsored by the University of Kentucky College of Medicine and MedLogix Communications, LLC.

MedLogix Communications, LLC

VALEANT™ Pharmaceuticals North America

This activity is supported by an unrestricted educational grant provided by Valeant Pharmaceuticals.

PROGRAM OVERVIEW

Febrile seizures are the most common type of seizure in children. Brief febrile seizures are now thought to be a relatively benign syndrome. While children who have experienced them are slightly more likely than other children to later develop unprovoked seizures and epilepsy, the febrile seizures are most likely a marker for, rather than a cause of, the subsequent seizures. Thus, a history of febrile seizures is present in many individuals who have epilepsy or unprovoked seizures. Prolonged febrile seizures, on the other hand, are less benign and have been linked with acute hippocampal injury and subsequent mesial temporal sclerosis and temporal lobe epilepsy, although the details of the frequency with which this happens are still being investigated. Given that prolonged febrile seizures are of the most concern, the current approach to treating febrile seizures focuses on preventing prolonged febrile seizures. This monograph is designed to review current literature regarding febrile seizures in order to provide physicians with the tools and information needed to make the best decisions for their pediatric patients with febrile seizures.

INTRODUCTION

The National Institutes of Health (NIH) Consensus Conference 1980 statement[1] and the International League Against Epilepsy (ILAE)[2] define a febrile seizure as a seizure event of infancy and childhood that is associated with fever; the definition excludes prior unprovoked seizures and seizures associated with acute central nervous system (CNS) infection, electrolyte imbalance, and other acute symptomatic events. The peak body temperature associated with the febrile illness must be ≥101°F, although fever may be absent during the febrile seizure.[3] Epidemiological studies have indicated that febrile seizures are age-specific occurrences, with most episodes occurring when children are between the ages of 3 months and 5 years. Febrile seizures can occur in children as young as 1 month of age and have a peak incidence at about 18 months of age[1,2,4]; onset of febrile seizures after the age of 7 does occur, but it is rare.[4]

Febrile seizures are classified as either simple or complex. Simple febrile seizures include those that are isolated, generalized, and brief.[3] Complex febrile seizures are focal, multiple (ie, more than one seizure during the febrile illness), or prolonged (ie, lasting longer than either 10 minutes[5-8] or 15 minutes).[3,8] In the case of extremely prolonged febrile seizures, which last longer than 30 minutes, they then meet the criteria for both complex febrile seizures and febrile status epilepticus.[9-11] When categorizing a febrile seizure as simple or complex, a child's prior neurological condition is not considered; however, children with neurological abnormalities are more likely to have a complex febrile seizure and to develop subsequent epilepsy than are children who are neurologically normal.

Statement of purpose

The objectives of this activity are to review the risk factors, pathophysiology, and prognosis associated with simple and complex febrile seizures and to describe the treatments available for the cessation of seizures and the prevention of future seizures.

EPIDEMIOLOGY

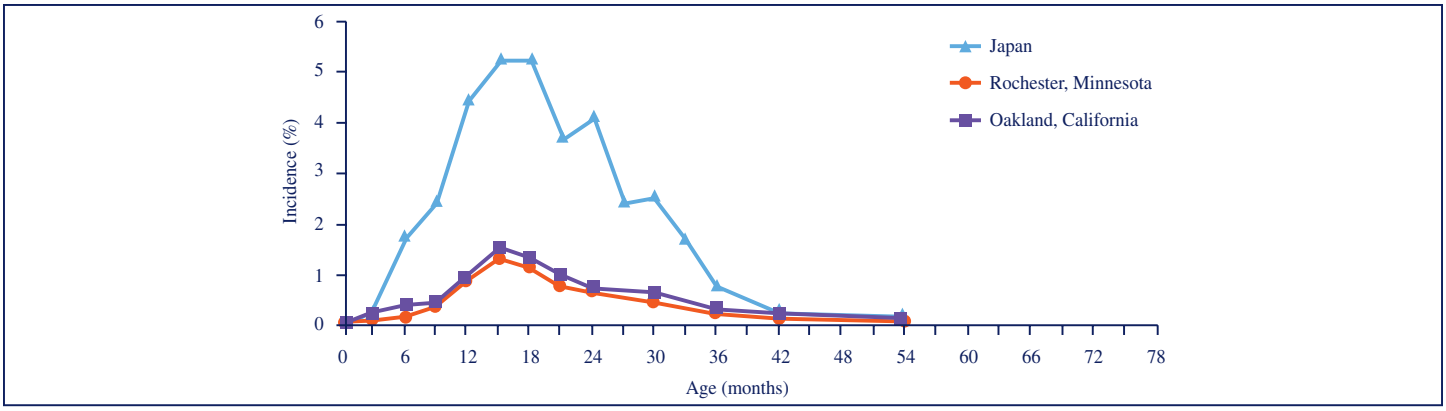
Febrile seizure is the most common seizure disorder in childhood,[4,12] with a worldwide incidence of approximately 2% to 5% (Table 1).[13-15] The incidence of febrile seizures varies by geographic location: incidences up to 8.8% and 14% have been reported in Japan and Guam, respectively.[13] Additionally, the peak incidence of febrile seizures occurs at the age of 18 months (Figure 1).[3,13]

Most febrile seizures are simple, but approximately one-third of febrile seizures will have 1 or more with complex features.[6,7] In a study of 428 children with a first febrile seizure, complex features were seen in 35% of children and included focality (16%), multiple seizures (14%), and prolonged duration (ie, >10 minutes; 13%).[7] Furthermore, 5% of the total group experienced febrile status epilepticus, defined as a febrile seizure lasting 30 minutes or longer.[7] Although febrile status epilepticus occurs infrequently, these seizures account for approximately one-quarter of all episodes of childhood status epilepticus.[9-11]

Table 1. *Worldwide Incidence of Febrile Seizures*[13-15]

Location	Percentage of Population Affected
China	0.5-1.5
Mexico	1.2
Rochester, MN	2.0
Oakland, CA	2.2
Great Britain	2.3
Denmark	3.24
Chile	4
Finland	6.9
Japan	8.8
Guam	14

Figure 1. *Incidence of febrile seizures by age in children in Japan; Rochester, Minnesota; and Oakland, California. [Reproduced with permission from Epilepsia.[13]]*



Although febrile seizures are associated with a febrile illness, the majority of febrile seizures do not occur at the onset of fever. For example, in a cohort of 347 children, Berg et al[6] found that 21% of children experienced seizures within 1 hour of recognition of fever onset, whereas 57% of children experienced a seizure between 1 and 24 hours after the recognized onset of fever, and 22% had their febrile seizure after more than 24 hours of recognized fever. Conversely, as the definition of "associated with a febrile illness" implies,[1,2] the child is not necessarily febrile at the time of the seizure but may develop the fever a few hours later.[6]

RISK FACTORS FOR A FIRST FEBRILE SEIZURE

A number of factors have been known to increase a child's risk of having a first febrile seizure. Using a multivariate analysis, Bethune et al[17] identified several important predictors of first febrile seizures, including family history in a first- or second-degree relative, attendance at day care, a neonatal discharge time of 28 days or more, and parental perception of slow development (Table 2). Having more than 1 of these risk factors may further increase a child's risk of a first febrile seizure. However, although having these risk factors substantially increases the risk of having a febrile seizure, it is important to remember that more than 50% of affected children had no risk factors.

Berg et al[18] used a matched case control study design to identify risk factors for a first febrile seizure among febrile children, with a particular focus on characteristics of the acute illness episode. Significant independent risk factors included height of temperature, family history of febrile seizures in a first- or higher-degree relative, and any maternal smoking during pregnancy (Table 3). Additionally, gastroenteritis as the cause of the fever was less likely to be associated with a febrile seizure than were other causes of fever (Table 3). As children were matched for age, this variable, which is known to be important (Figure 1), does not appear in the analysis of risk factors.

Table 2. *Absolute Risk of an Individual Child Developing Febrile Seizures Given a Population Incidence of 4%*[17]

Risk Factor	Risk (%)
Absence of all risks	2.2
Day care	6.6
Febrile seizure in a second-degree relative	7.7
Slow development	10.3
Neonatal discharge ≥28 days	11.6
Febrile seizure in a first-degree relative	
1 relative	9.6
2 relatives	32.5
Any 2 risk factors	28[a]
Range	20-73[b]

[a] Using a weighted average of risk factors.
[b] Range of risk given 2 lowest and highest risks.
[Reproduced with permission from *JAMA & Archives*.[17]]

Table 3. *Risk Factors for Which Child with a Febrile Illness Will Experience a Febrile Seizure*[18]

Risk Factor	Adjusted mOR*	95% CI	*p* Value
Peak Temperature	1.7	1.1-2.5	0.008
Gastroenteritis	0.1	0.0-0.5	0.006
Family history			
Febrile seizures in a first-degree relative	4.8	1.3-18.6	0.022
Febrile seizures in a second- or higher-degree relative	4.5	1.2-16.6	0.024
Any maternal smoking during pregnancy	3.0	1.0-9.0	0.051

Abbreviations: mOR, matched odds ratio; CI, confidence interval.
*For Peak Temperature, this quantity refers to the adjusted mOR per each increase in degree Fahrenheit above 101 degrees Fahrenheit.
[Reproduced with permission from Blackwell Publishing.[18]]

In addition to the risk factors discussed above, the nature of the infection is also important. As noted above, having gastroenteritis as the cause of the fever is associated with a lower risk of febrile seizures.[18] On the other hand, human herpesvirus has been shown to be a common etiological cause of febrile seizures.[19] HHV-6 infections account for approximately one-quarter of all first-time febrile seizures[19-22] and approximately one-third of first-time febrile seizures in children younger than 2 years.[23] Because HHV-6 and HHV-7 are neuroinvasive, they have been implicated in hippocampal injury.[19] Recently, results from an analysis of patients with prolonged febrile seizures (FEBSTAT study) demonstrated that HHV-6 and HHV-7 are common causes of prolonged febrile seizures.[24]

RISK FACTORS FOR RECURRENT FEBRILE SEIZURES

Recurrent febrile seizures occur in 30% to 40% of children.[5-7,25-31] In a prospective cohort study,[6,30] 428 children with a first febrile seizure were followed up for a median of 29 months (range, 2-44 months). By the time of the final follow-up, 31.8% of children had at least 1 recurrence of seizure; among these children, 75% of recurrent seizures occurred within 2 years of the initial febrile seizure (Figure 2). In this study the reported risk factors were (1) family history of febrile seizures, (2) young age (≤18 months) at the time of the first febrile seizure, (3) low peak body temperature (≤101.0°F), and (4) short duration of fever (≤1 hour). Family history of febrile seizures and a young age have consistently been associated with recurrent febrile seizures.[6,25-28,30,31] The relationship between risk of recurrent febrile seizures and young age is thought to be due to the duration of time in which a younger child will be in the age group at highest risk for febrile seizures, and not to an increased tendency to experience recurrent seizures before 18 months of age.[27,28,32]

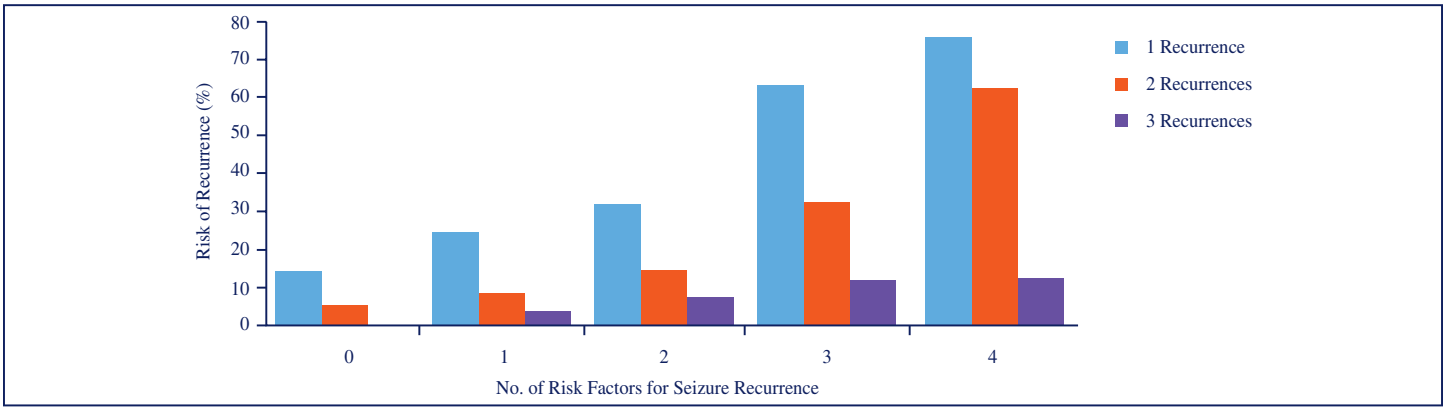
Additionally, low peak body temperature (≤101.0°F) has been associated with an increased risk of recurrent febrile seizures in a few studies (Table 4).[6,30,31,33] Pavlidou et al[31] observed a 46% recurrence risk (median follow-up, 4.3 years) in children with a peak body temperature <102°F and a 30% recurrence risk in children with a peak body temperature ≥102°F. Similarly, el-Rahdi and Banejeh[33] found that in children with the lowest fevers, from 100.4°F to 102.0°F, the rate of recurrence of seizures was 77%, compared to a recurrence rate of 8% in children with high fevers (≥102.2°F). It should be noted that the increased risk associated with peak body temperature is the temperature during the illness, not the temperature at the time of seizure. Short duration of recognized fever as a risk factor was only reported in one study,[6,30] but this factor was not specifically examined in the other studies.

Table 4. *Factors Associated With Recurrent Febrile Seizures*

Risk Factors
Age ≤18 months[6,25-28,31,32]
Peak temperature ≤101°F[6,30,31,33]
Family history of febrile seizures[6,25-28,30,31]
Duration of recognized fever <1 h[6,30]

The risk of recurrent seizures increases with the number of risk factors present (Figure 2).[30] In children with 2, 3, or 4 risk factors, the risk of recurrent seizures within 2 years of the first seizure is approximately 32%, 64%, and 75%, respectively. Furthermore, in children with prolonged febrile seizures who experience recurrent seizures, the subsequent seizures are likely to also be prolonged.[7,30] Notably, Berg and Shinnar[7] found that although having a prolonged febrile seizure did not increase the risk of recurrence, it did increase the chance of the recurrent febrile seizure being prolonged. Compared with children whose initial febrile seizure had been simple, children whose initial febrile seizure had been prolonged and who had a recurrent febrile seizure had a 2 to 4 times increase in risk of the recurrent seizure being prolonged.

Figure 2. *Percentage of recurrences 2 years after the initial febrile seizure, depending on the number of risk factors present. [Reprinted with permission from JAMA & Archives.[30]]*



Although children with a family history of epilepsy have a higher risk of developing subsequent epilepsy, most studies have found no difference in the risk of recurrence of febrile seizures between children with a family history of epilepsy and those without this history.[6,25,27,28,30] As with the risk of a first febrile seizure, neurodevelopmental abnormality, history of complex febrile seizures, ethnicity, and sex are not factors associated with an increased risk of recurrent febrile seizures.[6,7,25-28,30]

RISK FACTORS FOR EPILEPSY AFTER FEBRILE SEIZURES

The cumulative risk of epilepsy in individuals with a history of febrile seizures is 2% to 10%, which is somewhat higher than the cumulative risk of epilepsy in the general population.[5,16,26,34,35] Of the 5 large cohort studies on which this evidence is based, the highest risk of epilepsy was reported by Annegers et al,[5] in which follow-up exceeded 20 years. The recurrence risk in all studies is similar for the first few years, indicating that the increased risk reported by Annegers et al[5] is simply due to a much longer observation period. Overall, there appears to be only a modest increase in risk of epilepsy in patients with a history of febrile seizures.[5,26] In a prospective study of 428 patients with a history of febrile seizures (followed up for ≥2 years), 6% experienced a subsequent unprovoked seizure.[16] A family history of epilepsy, the occurrence of prolonged or complex febrile seizures, the presence of neurodevelopmental abnormalities, and a brief duration of fever before the initial febrile seizure were all associated with an increased risk of developing epilepsy after febrile seizures.[16] In an analysis of the Rochester Epidemiology Project in Rochester, Minnesota, (median follow-up of 18 years) data,[5] 687 children were identified as having had febrile seizures, of which 32 children (4.7%) experienced unprovoked seizures. Characteristics of the initial febrile seizure that were associated with subsequent recurrent unprovoked seizures included focality of the seizure, repeated seizures within the same febrile illness, seizure duration >10 minutes (ie, prolonged), and seizure occurrence at age <1 year or >3 years. Similarly, in the National Collaborative Perinatal Project (NCPP),[34] the occurrence of subsequent recurrent unprovoked seizures was greatest in children whose prior neurological or developmental status was suspect or abnormal and whose first seizure was complex.

The types of epilepsy that occur in children who have had febrile seizures vary, but they are not different from the types that occur in children without a history of febrile seizures. In the majority of cases, a causal relationship is unlikely. In populations with a high incidence of febrile seizures (eg, Tokyo, Japan; 10%),[13] there is not an increased incidence of epilepsy. Furthermore, there is no evidence that treatment or prevention of febrile seizures alters the risk of subsequent epilepsy[16,29,30,36] Approximately 10% to 20% of children with childhood-onset epilepsy have a prior history of febrile seizures.[5,7,26,37] This includes syndromes such as benign rolandic epilepsy and childhood absence epilepsy, where the relationship is clearly not causal. However, although in most cases febrile seizures are a marker for rather than a cause of subsequent epilepsy, recent data have shown that there is a link between very prolonged febrile seizures (ie, febrile status epilepticus) and temporal lobe epilepsy,[38] as these seizures are associated with hippocampal injury and subsequent mesial temporal sclerosis (MTS).[39]

MORBIDITY AND MORTALITY

Overall, morbidity and mortality are extremely low with febrile seizures. Multiple studies have demonstrated that children who experience febrile seizures have no permanent motor deficits, no deterioration of cognitive abilities (eg, cognitive performance, IQ score, or academic achievement),[36,40-44] and no deaths have been directly associated with febrile seizures in any of the large cohort studies, including the National Collaborative Perinatal Project (NCPP),[26,34] the British Child Health and Education Study,[43,45] and others.[10,40,46]

In the NCPP study[44] of long-term outcomes for children with febrile seizures, one sibling in each of 431 sibling pairs had experienced febrile seizures. There were no differences in IQ scores between children with febrile seizures and their paired sibling (mean difference, 0.7; SD, 13.4). Furthermore, no differences in IQ scores were seen between siblings in pairs in which the febrile seizures were recurrent (n=135), complex (n=145), or prolonged (ie, febrile status epilepticus; n=37). In the British Child Health and Education Study,[43] the authors examined 14,676 children born in one week during April 1970 for outcomes after febrile seizures; 12,981 individuals were included as controls. In total, 381 children had febrile convulsions: 287 (75%) had simple febrile seizures, and 94 (25%) had complex febrile seizures. In this study, children with febrile seizures (including complex and recurrent convulsions) performed as well as controls did in terms of academic progress, IQ score, and behavior at age 10 years. In another study, a Taiwanese cohort[41] of 4030 live births from 1989 to 1990, children were followed up to the age of 6 years. A survey of these children resulted in the identification of 103 children who had had at least one febrile seizure by the age of 3 years. Tests of achievement, attention, behavior, and memory were given to the children with febrile seizures and to 87 population-based controls. The group of children with febrile seizures scored significantly higher on the achievement test, had fewer missing errors and commission errors, and displayed no neurocognitive impairment in any other measures.

GENETICS

Febrile seizures are a classic example of the interaction of environmental factors (fever) and predisposition. As discussed in the section on risk factors for initial and recurrent febrile seizures, genetic predisposition clearly has a major role as a family history of febrile seizures is a major risk factor for having febrile seizures. Further evidence of genetic predisposition comes from twins studies. In a study of 673 sibling pairs, Tsuboi[47] reported a 56% concordance rate of febrile seizures in monozygotic twins and a 14% concordance rate in dizygotic twins. Correlation of clinical symptoms such as age of onset and peak body temperature was also greater in twin pairs than it was in non-twins. The data are most consistent with a familial predisposition suggesting a multifactorial mode of inheritance. However, a subset of children has been found with an autosomal dominant mode of inheritance.[48,49]

Although a number of single gene mutations, such as those affecting GABA and sodium channels, have been identified, these gene mutations account for only 1% to 2% of occurrences of febrile seizures (Table 5).[50-58] For example, in a genotyping study of 47 children with a history of febrile seizures (n=14), generalized epilepsy with febrile seizures (n=22), or childhood absence epilepsy (n=11), Audenaert et al[52] found a novel gene mutation in exon 4 of *GABRG2* (c.529C>G) in 1 of 14 individuals with febrile seizures. This mutation was not found in individuals with generalized epilepsy with febrile seizures or with childhood absence epilepsy. In another study, genotyping of 59 families with a total of 233 members, of which 112 were children who had a history of febrile seizures, revealed a febrile seizure linkage to chromosome 18 (18p11.2). This region of chromosome 18 includes the myo-inositol-1(or 4)-monophosphatase 2 (*IMPA2*) gene; the product of this gene plays a crucial role in the phosphatidylinositol signaling pathway.[58] Other genetic linkages have also been identified in individuals with febrile seizures, including 6 febrile seizure susceptibility genes (*FEB1-FEB6*) and genes encoding for voltage-gated sodium channel subunits α1, α2, and β1 (*SCN1A, SCN2A,* and *SCN1B*).[50,54] It should be emphasized that, although these mutations are of interest and may help us understand the pathophysiology of febrile seizures, all combined they account for a tiny proportion of children with febrile seizures.

Table 5. *Genetic Linkages to Febrile Seizures*[50-58]

Phenotype	Gene Location	Gene	Gene Product Function
Generalized epilepsy with febrile seizures plus (GEFS+)	2q24 19q13 2q24 5q24	*SCN1A* *SCN1B* *SCN2A* *GABRG2*	Na^+ channel subunit Na^+ channel subunit Na^+ channel subunit $GABA_A$ receptor subunit
Febrile seizures	17q11.2 8q13-q21 19p 2q23-24 5q14-15 6q22-24	*SEZ-6* None identified	None identified None identified
Prolonged febrile seizures, hippocampal sclerosis, temporal lobe epilepsy	5q14-15	*IL1B-511T*	Interleukin
Febrile seizures, temporal lobe epilepsy, other seizure disorders	18qter 1q25-31	None identified	None identified

Abbreviation: GABA, γ-aminobutyric acid.

INITIAL EVALUATION

Evaluation of children with a febrile seizure should focus on excluding acute neurological conditions such as meningitis, encephalitis, and severe electrolyte imbalance. A detailed medical history and physical and neurologic examinations are necessary, and additional testing should be based on the patient's clinical condition and the suspected underlying cause of the febrile seizure.[9,59] Laboratory measures may be used to diagnose the underlying illness (eg, complete blood cell count, electrolytes, Ca^{2+}, and Mg^{2+}), but these tests are not typically useful in children older than 6 months unless there is a history of disease or physical findings (eg, diarrhea, vomiting, dehydration, low blood sugar).[60]

The definition of a febrile seizure excludes individuals who have meningitis or encephalitis. In most cases, this exclusion can be done clinically, based on history and examination. However, in some patients, a lumbar puncture (LP) should be performed to rule out meningitis or other acute neurologic illnesses.[4,9] Meningitis is found in 2% to 5% of children who present with what appears to be a febrile seizure.[59,61,62] An LP should be strongly considered if a child with a simple febrile seizure[4] is <12 months old. In addition, if the child is lethargic or has had prior antibiotic therapy, an LP is indicated. Clinical judgment should be used in children 12 to 18 months of age, with a low threshold for performing an LP. An LP should also be considered in children with a first febrile seizure above age 5 years to rule out encephalitis. In children with a complex febrile seizure, an LP should be strongly considered at any age.[4] In the absence of the risk factors listed above, most studies report a low yield with routine LP.[61,63] Given the high mortality of untreated meningitis and the low morbidity of an LP, when there is any doubt, an LP should be performed.

Electroencephalography (EEG) and imaging tests may be performed in the evaluation of children with seizure disroders.[4,60] However, in children with febrile seizures, an EEG is generally not useful for the evaluation of simple febrile seizures and is of unclear value for complex febrile seizures, with the exception of very prolonged ones.[59,64,65] There is no clear evidence that the EEG is useful in predicting the recurrence of seizures or the development of epilepsy in children with simple febrile seizures.[65] Imaging studies are also of very limited value for the evaluation of febrile seizures, with the exception of status epilepticus. Furthermore, skull x-rays are of no use, and computed tomography scans are of limited use, unless there is a concern about intracranial pressure or trauma. When imaging is done, magnetic resonance imaging (MRI) is the procedure of choice,[9] and in cases of febrile status epilepticus, MRI has been able to detect evidence of acute hippocampal injury, as well as of related abnormalities.[66,67] However, at this point in time, MRI is not part of the routine evaluation of febrile seizures—including evaluation of complex seizures. Conversely, MRI is considered part of the assessment of status epilepticus of any type.[68]

PATHOPHYSIOLOGY

Febrile seizures are an age-specific occurrence, in which there is an age-dependent increased susceptibility to seizures induced by fever. Fever is the natural response to inflammation and infection; however, the detailed mechanism by which fever induces seizures remains unclear. Although CNS infections are excluded in the definition of febrile seizure, the nature of the underlying illness does appear to have a role. Gastroenteritis is associated with a lower risk of febrile seizures than are other common infectious illnesses (eg, otitis media and invasive bacterial infection),[18] and herpesvirus-6 and herpesvirus-7 infections have had a high reported rate of association with febrile seizures.[4,20,23,69] Further evidence that fever is not the sole cause is the fact that, as discussed above, although all cases occur in the context of a febrile illness, fever is not present at the time of the seizure in a significant minority of cases.[3,6]

It was previously thought that a key factor in producing a febrile seizure was the rate of rise in body temperature; however, more recent data suggest that this is not the case.[70] Many children have their seizure either when not yet febrile or after a fever lasting for hours. The magnitude of the peak body temperature has a greater association with the risk of febrile seizures.[70,71]

Recent data suggest that proinflammatory cytokines, age-specific factors, and the underlying cause of fever have roles in producing seizure during a febrile illness. Proinflammatory cytokines are released in response to cellular damage and infection.[72] These cytokines, including interleukin-1β (IL-1β), act as pyrogens to cause fever, and have they been shown to have a role in seizure disorders. Proinflammatory cytokines have also been shown to affect neuronal excitability,[72] suggesting a role for cytokines in altering synaptic transmission in seizure disorders.[73] In an experimental model of seizure, Dubé et al[72] showed that intracerebral application of high doses of IL-1β can cause spontaneous seizures, even in the absence of hyperthermia. Furthermore, other studies have demonstrated that intracerebral application of IL-1β enhances epileptic activity, whereas its receptor antagonist (IL-1Ra) mediates anticonvulsant actions.[73,74] In humans, increased production of IL-1β has been found specifically in the cerebral spinal fluid of children with febrile seizures and in patients with temporal lobe epilepsy with hippocampal sclerosis.[75,76] Additionally, IL-1β is an *N*-methyl-D-aspartate (NMDA) receptor agonist and, therefore, is a proconvulsant.[75] Altogether, these data indicate that IL-1β has a proconvulsive effect that may contribute to the mechanism of febrile seizures.

In humans the cytokine chiefly responsible for the febrile response is IL-1β.[74] Interleukin-1β is an NMDA agonist and, thus, is proconvulsant. It may well be associated with the mechanism of febrile seizures, and this may explain, in part, why it is peak temperature, rather than the temperature at the time of the seizure, which correlates with the degree of cytokine release associated with the risk of a febrile convulsion.

Animal studies have shown that increases in temperature influence numerous cellular processes, including neuronal excitability, and the functions of several neuronal ion channels are affected by temperature in both physiological and hyperthermic ranges.[77] Thus, an increase in brain temperature could enhance the rate, magnitude, or pattern of neuronal firing, leading to seizures.[77] Baram et al[78] developed an age-appropriate animal model that uses immature mice to mimic the condition seen in children, and this model has been useful in providing insights into the pathophysiology and physiologic consequences of febrile seizures. In this model, febrile seizures appear to be of limbic origin.[78-81] In studies that used this model, febrile seizures lasting longer than 19 minutes did not result in cell death[81]; however, these prolonged seizures were associated with long-lasting changes in h-channels.[82] The h-channel is the hyperpolarization-activated cation channel (the pacemaker channel), which can be either excitatory or inhibitory.[83] Changes in h-channels have also been associated with increased susceptibility to seizures: in the rat febrile seizure model, h-channel activity leads to an enhanced hyperpolarization-activated conductance in CA1 pyramidal cells, which is key to the formation of a hyperexcitable hippocampus.[84,85]

Other animal studies of febrile seizures have also shown the effects of temperature on the development of febrile seizures and hippocampal damage.[78,86,87] Using in vitro preparations, Tancredi et al[88] demonstrated an age-dependent induction of epileptiform activity by increasing temperatures in hippocampal slices from young rats aged <4 days, 4-28 days, and >28 days. In slices from rats aged <4 days or >28 days, epileptiform activity was detected when the temperature was raised above 100.8°F, but ceased when the temperature returned to control values (ie, 95°F-96.8°F). In contrast, in slices from rats between the ages of 4 and 28 days, epileptiform activity continued for up to 2 hours when the temperature was decreased to control values. Although the use of animal models has led to important discoveries about the cellular processes affected by hypothermia and proinflammatory cytokines and their relationship to seizure, much remains to be elucidated about the pathophysiologic mechanisms of febrile seizures.

FEBRILE SEIZURES AND MESIAL TEMPORAL SCLEROSIS

Febrile seizures have been associated with MTS[3,4,62,89,90]; however, whether febrile seizures can lead to MTS or temporal lobe epilepsy is controversial. Retrospective studies show that some patients with intractable epilepsy and MTS had a history of febrile seizures in childhood.[39,66,68,91] In a study of 6 families that each had 4 or more members with a history of febrile seizures, 14% of individuals (8 out of 59) with a history of febrile seizures developed temporal lobe epilepsy, and only 1 out of 213 individuals without a history of febrile seizures developed temporal lobe epilepsy.[92]

Several studies, both in animal models of febrile seizures and in clinical settings, suggest that there is a link between prolonged febrile seizures and the development of hippocampal injury and, subsequently, epilepsy.[67,78-82,87,93] Animal models of febrile seizures show an age-dependent effect[78,87] and long-lasting changes in hippocampal circuits following prolonged febrile seizures.[78-81] In a model of febrile seizures in immature rats, Baram et al[78] demonstrated that hyperthermia caused seizures in 94% of 10- to 11-day-old rats. Electroencephalography recordings revealed that seizure activity was absent in the cortex but present in the hippocampus and amygdala. This group of investigators has also shown that prolonged febrile seizures in immature rats caused long-term changes in excitability in the limbic system.[79,80]

Prolonged febrile seizures and febrile status epilepticus have been associated with MTS. VanLandingham et al[66] assessed the MRIs of 27 children who had experienced a complex febrile seizure (Figure 3). Acute changes on MRI were observed in some of the patients with prolonged seizures (mean seizure duration, 90 minutes) and were followed by later long-lasting changes that were associated with MTS. Although MRI changes were seen in only a small number of these cases, no changes were seen on MRIs of children with generalized (ie, not prolonged) febrile seizures. Thus, it remains unknown whether febrile seizure is a causal factor in the development of epilepsy or MTS. In general, febrile seizures are associated with only a minority of cases of MTS, and most evidence suggests multiple etiologies for MTS.[68] Results from Maher and MacLachlan,[92] VanLandingham et al,[66] and others[93-95] have led to the theory that preexisting pathology is responsible for triggering prolonged or focal seizures, thereby causing the brain to be more susceptible to seizure-induced damage and subsequent MTS.

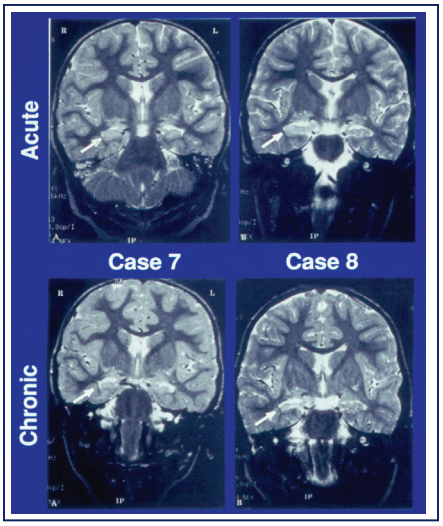


Figure 3. *Acute and chronic MRI changes after febrile seizure. Case 7 is a 28-month-old girl who had a fever for 10 days, with the diagnosis of bilateral otitis media; she experienced 5 seizures, and MRI was performed 24 hours after the first seizure. Case 8 is a 30-month-old child with a history of simple febrile seizures; while suffering from an upper respiratory tract infection, the child had 3 complex febrile seizures of 5, 17, and 50 minutes in duration during a period of 2 hours. MRI was performed in this child 2 days after the seizures. [Reprinted with permission from Annals of Neurology].*[66]

The FEBSTAT study,[96] an ongoing, prospective, multicenter study, will examine the outcomes of prolonged febrile seizures. This study will recruit 200 children (aged 1 month through 5 years) who are identified as having a febrile seizure lasting 30 minutes or longer. Procedures include MRI and EEG within 72 hours of the seizure; virology studies within 72 hours and at 1 month; baseline neuropsychological testing at 1 month; and repeat of MRI, EEG, and neuropsychological testing at 1 year, 5 years, and at development of epilepsy. Some of the clinical characteristics of the first 119 cases (Table 6) were recently published.[96] Prolonged febrile seizures were generally seen in children who were very young (median age, 1.3 years), had a family history of febrile seizures, and had a high peak body temperature (mean peak body temperature, >103.2°F). Additionally, prolonged febrile seizures usually did not stop spontaneously: 87% of seizures ceased only after the administration of additional treatment with a benzodiazepine class drug. This suggests that before the ready availability of benzodiazepines, prolonged febrile seizures were likely to be even more prolonged. In the long run, it is hoped that the ongoing prospective FEBSTAT study, which is following up these children long-term, will provide more definitive answers about the relationship between prolonged febrile seizures and temporal lobe epilepsy.

Table 6. *Results of FEBSTAT Study*[96]

Characteristics of the Illness and Febrile Seizures (n=119)	Number (%)
Peak temperature during illness (mean, 103.2°F)	
101.0°F -101.9°F	18 (15.1)
102.0°F -102.9°F	39 (32.8)
103.0°F -103.9°F	27 (22.7)
≥104.0°F	35 (29.4)
Seizure duration (mean, 68 min; range, 30-240 min)	
30-59 min	53 (44.5)
60-89 min	26 (21.9)
90-119 min	12 (10.1)
120-239 min	25 (21.0)
≥240 min	3 (2.5)
Continuous vs intermittent	
Continuous	62 (52.0)
Intermittent	57 (48.0)
Generalized vs focal	
Generalized	26 (21.8)
Focal	93 (78.2)

[Reproduced with permission from Lippincott Williams & Wilkins.[96]]

TREATMENT

Current approaches to the management of febrile seizures are based on evidence from epidemiological studies that show that, with the exception of very prolonged seizures, most febrile seizures are benign. The majority of children who experience a simple febrile seizure do not need drug treatment; thus, most cases are simply followed up by counseling and educating parents. In those children who do need treatment because of an increased risk of morbidity, such as those who experience prolonged or repetitive complex febrile seizures, intervention is typically focused on abortive treatment.

Stopping a febrile seizure

The majority of febrile seizures are short and stop on their own with no treatment. When treatment is indicated, abortive therapy with a benzodiazepine at the time of the febrile seizure is the treatment of choice (Table 7).[97-103] If the febrile seizure is still ongoing when the child arrives in the emergency department, treatment to terminate the seizure is mandatory. Benzodiazepines such as diazepam (intravenous [IV] and rectal), lorazepam (IV), and midazolam (intranasal and buccal) are effective in most cases.[9,97,102,104,105] Rectal diazepam and intranasal midazolam are also useful when IV access is difficult in the ambulance or emergency department.[9,97]

Rectal diazepam terminates approximately 80% to 90% of seizures in patients with simple febrile seizures, complex febrile seizures, status epilepticus, or epilepsy[97-99] and stops the majority of seizures in less than 10 minutes. In a prospective study of 37 cases of childhood status epilepticus, 10 of which involved febrile seizures, rectal diazepam and IV diazepam were both effective in stopping seizures.[98] Patients received rectal diazepam (0.16-0.57 mg/kg; n=16), IV diazepam (0.04-0.33 mg/kg; n=15), or no drug therapy (n=6). Because of transport times, all study drugs were administered by paramedics before the patient arrived at the hospital. All patients treated with IV diazepam and 81% of patients treated with rectal diazepam stopped seizing within 10 minutes of diazepam administration; however, seizures recurred shortly after first treatment in 30.8% of children who received rectal diazepam.

Randomized controlled studies of midazolam use in the emergency department and home settings have shown that it is safe and effective in stopping febrile seizures in less than 5 to 10 minutes.[100,102,105,106] In one randomized controlled study, McIntyre et al[102] found that treatment was successful in 56% of cases (61 of 109) with buccal midazolam use and 27% of cases (30 of 110) with rectal diazepam use. Similarly, Fişgin et al[105] showed that intranasal midazolam was effective within 10 minutes in 87% of cases, whereas rectal diazepam was effective within 10 minutes of administration in 60% of cases. It should be noted, however, that there is no true nasal preparation of midazolam available, and there has been little experience in the United States with the use of midazolam solution intranasally.

If the seizure continues after an adequate dose of a benzodiazepine, treatment should proceed with a protocol for treating febrile status epilepticus.[9] Although IV lorazepam is very effective, rectal administration of lorazepam solution is generally less effective because it is not absorbed sufficiently. The side effects most commonly reported with benzodiazepines are minor and include slight impairment in cognitive function,[107] ataxia, and irritability.[108] The risk of respiratory depression with rectal diazepam appears to be very low.[109]

For seizures occurring at home that require intervention, abortive therapy can also be used at home. Rectal diazepam is the treatment of choice in the home setting,[7,103,110,111] and parents can be taught its proper use for aborting seizures or for preventing seizures during a febrile illness.[63,99] However, routine use of diazepam to abort or prevent febrile seizures is not recommended, as most febrile seizures are brief and self-limited.[112] In one study, Rossi et al[112] followed up 72 children, after a first febrile seizure, for at least 22 months, during which time parents were educated about febrile seizures and instructed on how to use rectal diazepam (5 or 10 mg) at the onset of seizure. Recurrent seizures occurred in 20 children, and the parents of 14 of these patients reported that they were less fearful during the second episode. Furthermore, 80% of the 91 families enrolled in the study experienced psychological benefits (eg, positive subjective feelings) from having rectal diazepam available.

Having rectal diazepam available at home has the effect of improving quality of life and reducing stress regardless of whether the diazepam is actually used.[103] However, this approach is not recommended for all patients. Candidates for the use of rectal diazepam therapy in the home setting to abort or prevent febrile seizures (ie, at time of seizure or fever) include patients with the following characteristics[62,103,110,111]

- Prolonged or repetitive complex seizures
- High risk of febrile seizure recurrence
- Residence far away from medical care

Table 7. *Studies of AEDs for Abortive Therapy at Time of Febrile Seizure*

Reference	Study Design	Outcomes	Adverse Effects
Knudsen[97]	• Prospective study of 44 children with febrile seizures or epilepsy treated with rectal diazepam (0.5-0.9 mg/kg)	• Seizures ceased in ≤10 min in 87% of cases (47/54) treated with rectal diazepam • Seizures recurred within 15 min in 12% of cases (7/59)	Mild sedation
Dieckmann[98]	• 37 cases of childhood status epilepticus, 10 of which were febrile seizures • Patients received rectal diazepam (0.16-0.57 mg/kg; n=16), IV diazepam (0.04-0.33 mg/kg; n=15), or no drug therapy (n=6) • Study drugs were administered by paramedics before patients arrived at the hospital	• 100% of patients treated with IV diazepam and 81% of patients treated with rectal diazepam stopped seizing within 10 min of administration	Respiratory depression
Camfield et al[99]	• Prospective trial of rectal diazepam • Parents of 30 children with seizure disorders (18 with a history of febrile seizures) were given rectal diazepam (0.5 mg/kg) to have on hand to abort future seizures	• 57% of children were given the drug; the remaining children either never had a second seizure or the seizure lasted less than 3 min • Seizures stopped within 5 min of administration of rectal diazepam in 15 of 17 children (88%)	None reported
Lahat et al[100]	• Prospective randomized study of 47 children with prolonged febrile seizures • 21 children received intranasal midazolam (0.2 mg/kg) for 26 episodes • 23 children received IV diazepam (0.3 mg/kg) for 26 episodes	• Both drugs stopped seizures within 10 min of treatment onset in 88.5% of seizures in the midazolam group and 92.3% of seizures in the diazepam group	None reported
Mahmoudian and Zadeh[101]	• Prospective randomized trial of 70 children with febrile or afebrile seizures • Intravenous diazepam (0.2 mg/kg; n=35) • Intranasal midazolam solution • (0.2 mg/kg; n=35)	• Seizures were controlled within 10 min of treatment onset in all patients (no difference between treatment groups) • The mean interval between treatment administration and seizure control was 3.58 min in the midazolam group and 2.94 min in the diazepam group • Time from seizure onset to treatment was faster in the midazolam group because the placement of an IV line was not necessary	None reported
McIntyre et al[102]	• Multicenter, randomized control trial comparing buccal midazolam with rectal diazepam for immediate treatment of febrile and afebrile seizures in children • 219 episodes in 177 patients • Midazolam (0.5 mg/kg; n=109 episodes in 92 patients) • Diazepam (0.5 mg/kg; n=110 episodes in 85 patients)	• Seizures were controlled within 10 min of treatment onset in 65% of episodes with midazolam vs 41% of episodes with diazepam (p<0.001) • 14% of midazolam-treated seizures vs 33% of diazepam-treated seizures recurred within 1 hour of the initial treatment (p=0.02)	Respiratory depression
O'Dell et al[103]	• Prospective study of 38 children with a history of seizures (14 with complex febrile seizures) who were treated at home with rectal diazepam at the time of prolonged or repetitive seizures • Patients were followed up for 6 mo	• Seizure recurrence experienced by 2 of 14 patients with complex febrile seizures and 17 of 24 patients with epilepsy/unprovoked seizures • 16 of 19 episodes (84%) that met criteria for treatment were stopped with rectal diazepam and no emergency department visit was required • Parents of children with febrile seizures reported a significant decrease in stress during the 6-mo study period (mean stress score, 3.0 ± 0) vs the preceding 6 months (mean stress score, 5.3 ± 0.8; p<0.0001)	Mild sedation

Abbreviations: AED, antiepileptic drug; IV, intravenous.

Preventing a febrile seizure

Although it would seem logical that aggressive treatment with antipyretics would reduce the risk of having a febrile seizure, there is little evidence to show that these drugs reduce the risk of febrile seizure recurrence.[18,71,113-115] Camfield et al[113] found that in patients who received aggressive antipyretic therapy the risk of recurrence was 25%. In another study, 50% of children who experienced a febrile seizure had received antipyretic medication before the seizure.[114] Despite the lack of evidence for the effectiveness of antipyretics in preventing febrile seizures, their use can make children feel more comfortable; thus, antipyretic therapy may be considered solely for this reason, as long as the agent has a low toxicity profile and is not overused.

Intermittent prophylaxis with benzodiazepines at the time of fever has been demonstrated to modestly reduce the recurrence of febrile seizures in some cases (Table 8).[29,108,116-119] In particular, diazepam (oral or rectal), because of its safety profile, effectiveness, and convenience, has been studied extensively for use as intermittent prophylaxis to prevent recurrent febrile seizures.[29,63,108,116-119]

The use of diazepam for intermittent prophylaxis was examined in one prospective study of 110 children who had experienced a previous febrile seizure. Oral diazepam (0.35 mg/kg every 8 hours; n=45) was administered prophylactically at the time of fever; control patients received no prophylaxis (n=65).[108] After at least 4 years of follow-up, seizures recurred in 11.1% of children who received oral diazepam prophylaxis and in 30.7% of children who did not receive prophylaxis ($p<0.05$). Unlike diazepam, other antiepileptic drugs (AEDs), such as phenobarbital, have been shown to be ineffective in reducing the risk of seizure recurrence when they are used for intermittent prophylaxis.[120] This is likely because these AEDs do not reach a therapeutic level in a short period of time. However, it should be noted that intermittent prophylaxis with diazepam (or any other AED) has not been shown to decrease the risk of development of subsequent epilepsy, and the potential for adverse events with AEDs often outweighs the minor risks associated with simple febrile seizures.[115] The author of this review rarely uses intermittent prophylactic therapies at time of illness or fever for management of febrile seizures, as it results in frequent use of benzodiazepines for a modest reduction in the frequency of recurrent febrile seizures.

Table 8. *Studies of AEDs for Intermittent Prophylaxis at Time of Fever*

Reference	Study Design	Outcomes	Adverse Effects
Verrotti et al[108]	• Prospective study of 110 children with a history of febrile seizures • Oral diazepam (0.35 mg/kg every 8 h), administered at the time of fever (n=45) • No prophylaxis (n=65) • Follow-up, ≥4 y	• Seizures recurred in 11.1% of children who received oral diazepam prophylaxis vs 30.7% of children who did not receive prophylaxis ($p<0.05$)	Ataxia, sedation, and irritability
Knudsen and Vestermark[116]	• Randomized clinical trial of 195 children with a first febrile seizure • Continuous treatment with phenobarbital (mean dose, 3.5 mg/kg/d; n=96) • Intermittent treatment with rectal diazepam (5 mg every 8 hours; n=99), when the child's temperature was ≥101.3°F	• Within 12 mo of the initial febrile seizure, 16% of children treated with intermittent diazepam prophylaxis had a seizure recurrence	None reported
Knudsen[29]	• Prospective, randomized trial of 289 children with febrile seizures • Rectal diazepam at the time of fever (n=152) or as abortive treatment at the time of seizure (n=137) • Patients were followed up for 18 mo • Doses for both groups were 5.0-7.5 mg	• Recurrent seizures – 33.6% of children in the abortive treatment group experienced recurrent seizures – 12.5% of the children who received intermittent prophylaxis experienced recurrent seizures	Sedation, ataxia, and irritability
Pavlidou et al[118]	• Long-term, prospective, randomized control study of rectal diazepam • 139 children with a first febrile seizure were randomly assigned – Rectal diazepam (0.33 mg/kg every 8 h on Day 1 of fever, then every 12 h on Day 2; n=68) – Controls (no diazepam; n=71) • Patients were followed up for 3 y	• In the first year, 29% of diazepam-treated patients experienced seizure recurrences (at least 1) vs 46% of controls • By the end of the third year, 35% of diazepam-treated patients experienced a second febrile seizure vs 60% of patients in the control group	Sedation and irritability
Rosman et al[119]	• Randomized, double-blind control study of 406 children with a history of febrile seizures • Oral diazepam (0.33 mg/kg every 8 h, starting at the time of fever; n=202) • Placebo (n=204) • Mean follow-up, 1.9 y	• There was a 44% decrease in the risk of seizure recurrence in the diazepam group (RR, 0.56; 95% CI, 0.38-0.81; $p=0.002$)	Ataxia, sedation, and irritability

Abbreviations: AED, antiepileptic drug; RR, rate ratio; CI, confidence interval.

Continuous prophylaxis to prevent febrile seizures, although rarely used or indicated in clinical practice, has been shown to be effective in reducing febrile seizure occurrence in some studies (Table 9).[113,116,120-126] Daily phenobarbital is effective in some cases[113,120,122-124]; however, long-term use is rarely indicated and has been associated with an increased rate of adverse effects, including impaired cognitive performance and behavioral abnormalities.[120,122,124,125] Valproate has also been shown to be effective for continuous prophylaxis by several studies.[121,123,125,127] However, valproate use is uncommon in the United States because of its association with fatal hepatotoxicity, particularly in young patients.[128] Carbamazepine and phenytoin—although effective for the treatment of epilepsy—have been shown to be ineffective for preventing recurrent febrile seizures.[62,122,124,126] There are no published data on the efficacy of newer AEDs (eg, gabapentin, lamotrigine, topiramate, tiagabine, or vigabatrin) as abortive or prophylactic therapy for febrile seizures.[62] The recommendations against the use of continuous prophylaxis for the management of febrile seizures are based on their risk-benefit assessment rather than lack of efficacy.[3,63,111,115]

Table 9. *Studies of AEDs for Continuous Prophylaxis in Febrile Seizures*

Reference	Study Design	Outcomes	Adverse Effects
Knudsen and Vestermark[116]	• See details in Table 8	• Within 6 mo of the initial febrile seizure, 11% of children treated with diazepam and 9% of children treated with phenobarbital experienced a recurrent seizure (NS) • Within 12 mo of the initial febrile seizure, 16% of children treated with diazepam and 15% of children treated with phenobarbital experienced a recurrent seizure (NS) • Recurrent seizures were similar in duration and severity for the groups	Phenobarbital: hyperkinesias and irritability; diazepam: transient sedation
Wolf et al[120]	• Prospective randomized study of 355 children with a history of febrile seizures • Continuous prophylaxis with phenobarbital (3-4 mg/kg/d; n=106) • Intermittent prophylaxis with phenobarbital (5 mg/kg/d; n=140) • No prophylaxis (n=109)	• No significant differences in seizure recurrence between children who received intermittent prophylaxis and those who received no prophylaxis • Seizure recurrence with continuous prophylaxis vs the other 2 groups combined: – 3% vs 9% at the 6-mo follow-up ($p<0.025$) – 8% vs 20% at the 12-mo follow-up ($p<0.005$) – 8% vs 26% at the 18-mo follow-up ($p<0.0001$)	Hyperactivity, irritability, rash, and lethargy
Wallace and Smith[121]	• Prospective study analyzing seizure recurrence during 184 consecutive 6-month periods in 108 children with a history of febrile seizures • Phenobarbital (4-5 mg/kg/d; n=45 periods), valproate (20-30 mg/kg/d; n=39 periods), or no treatment (n=100 periods)	• Seizures recurred in – 13.3% of the 6-month periods in 4 children who received phenobarbital and had optimal serum concentrations – 12.8% of 6-month periods in 5 children who received valproate and had optimal plasma concentrations – 34.0% periods in 24 children who received no treatment ($p<0.02$ for each treatment group vs no treatment)	Behavioral issues
Antony and Hawke[122]	• Double-blind prospective trial • 40 children with recurrent or complex febrile seizures • Carbamazepine (20 mg/kg/d; n=19) • Phenobarbital (4-5 mg/kg/d; n=21)	• 47% of children in the carbamazepine group had recurrent seizures • 10% of phenobarbital-treated children had recurrent seizures ($p<0.05$)	32% of children treated with carbamazepine and 43% of children treated with phenobarbital had adverse effects
Mamelle et al[123]	• Prospective randomized trial of 69 patients with a first febrile seizure followed up for an average of 21 mo • Phenobarbital (3-4 mg/kg; n=21) • Valproate (30-40 mg/kg; n=22) • Placebo (n=26)	• After daily treatment, 14 children experienced seizure recurrence: 1 in the valproate group, 4 in the phenobarbital group, and 9 in the placebo group	None reported

Table 9. *Studies of AEDs for Continuous Prophylaxis in Febrile Seizures* (cont.)

Reference	Study Design	Outcomes	Adverse Effects
Bacon et al[124]	• 138 Children who had a first febrile seizure by age 2 y • Treated continuously for 12 mo • Phenobarbital (5 mg/kg/d, then adjusted to achieve salivary levels of 8-15 mg/L; n=48) • Phenytoin (8 mg/kg/d, then adjusted to salivary levels of 1-2 mg/L; n=47) • Placebo (n=43)	• 10/48 (21%) treated with phenobarbital had recurrent seizures • 16/47 (34%) treated with phenytoin had recurrent seizures • 15/43 (35%) receiving placebo had recurrent seizures	Rash in 1 child treated with phenobarbital; behavioral issues in all 3 groups
Lee and Melchior[125]	• Prospective study of 90 children with a first febrile seizure • Valproate (20-30 mg/kg/d); n=32) • Phenobarbital (3-5 mg/kg/d; n=33) • No treatment (n=25)	• Seizures recurred in 48% of untreated patients vs 13% of valproate-treated patients ($p<0.001$); 24% of phenobarbital-treated patients experienced recurrent seizures (difference from controls not significant)	Adverse effects were seen with phenobarbital, including hyperactivity and sleep disturbances
Camfield et al[113]	• Randomized double-blind study comparing phenobarbital (5 mg/kg/d; n=39) to placebo (n=40) for 12 mo	• 5.1% of patients treated with phenobarbital experienced at least 1 recurrent seizure vs 25% of controls ($p<0.02$)	None reported
Camfield et al[126]	• Prospective study of 16 children who required long-term prophylaxis for recurrent febrile seizures and had experienced failure of phenobarbital to prevent seizures or were intolerant to phenobarbital • Carbamazepine (10-15 mg/kg/d)	• 13/16 (81.3%) of patients experienced recurrent seizures within 18 months of starting carbamazepine	None reported

Abbreviations: AED, antiepileptic drug; NS, not significant.

Preventing future unprovoked seizures and epilepsy

Prevention of febrile seizures with AED therapy does not reduce the risk of developing future unprovoked seizures or epilepsy later in life.[36,63,89,129,130] In studies by Knudsen and colleagues,[36,117] intermittent prophylactic therapy with diazepam did not reduce the rate of subsequent epilepsy with follow-up of 12 years. Similarly, Wolf and colleagues[120,129] showed that although daily prophylaxis with phenobarbital resulted in a lower rate of febrile seizure recurrence,[120] this therapy did not reduce the rate of later unprovoked seizures with 10 years of follow-up.[129] In the study of intermittent diazepam at time of fever, Rosman et al[119] reported that there was a modest reduction in the rate of recurrent febrile seizures, but at follow-up, 2 years later there was no difference in the rate of developing epilepsy between the 2 groups.[131]

Treatment recommendations for simple febrile seizures

The American Academy of Pediatrics (AAP) recommendations for the management of simple febrile seizures were recently updated.[63] These guidelines emphasize that although several AEDs have been shown to reduce the risk of recurrence of febrile seizures, because most febrile seizures are brief (ie, under 10 minutes in duration), intervention is generally unnecessary and long-term therapy is not recommended. In lieu of drug treatment, the counseling and educating of parents are essential to managing febrile seizures.

Although most febrile seizures are benign and the neurologic outcome is excellent, these events are terrifying for most parents,[110,132,133] who sometimes think their child might die during the seizure.[133] The occurrence of febrile seizures can reduce the family's quality of life.[103,133] Parents may experience anxiety and fear whenever a child develops a fever.[103,133] Thus, parents and caregivers should be educated about febrile seizures as a common disorder of childhood. Explanations regarding the favorable prognosis, the type of seizure (ie, simple or complex) the child had, and the steps to take in the event of another seizure can reassure parents and improve their ability to cope with a recurrence.[110] The information presented may vary, depending on the parents' medical sophistication, and it is advisable that this information be given to the parents in both the emergency setting and at a later point, as it may be difficult for parents to absorb the information at the time of the initial crisis.

Treatment recommendations for complex and prolonged febrile seizures

Unlike the treatment of simple febrile seizures, the treatment of complex and in particular of prolonged febrile seizures is more controversial, given the increased potential for morbidity with these types of seizures. Whereas in the case of focal seizures, they are most likely a marker for future epilepsy, prolonged febrile seizures may cause hippocampal injury and subsequent epilepsy. Therefore, the focus of treatment is on preventing prolonged febrile seizures. Rectal diazepam rapidly and reliably terminates approximately 80% to 90% of febrile seizures, including complex febrile seizures and status epilepticus.[97-99] Thus, rectal diazepam may be useful in the prevention of prolonged seizures. In those cases where abortive treatment is indicated, the author prefers the use of rectal diazepam as an abortive agent at the time of a seizure, although other choices can be used.

CONCLUSIONS

Febrile seizure is the most common seizure type in childhood. The prognosis is generally favorable: children with febrile seizures do not show impaired cognition, and neurologic changes are uncommon. Any morbidity that does occur is most likely to be associated with prolonged seizures. However, more studies are needed on the relationship between extremely prolonged febrile seizures and MTS or temporal lobe epilepsy, including studies on treatment options that have the potential to reduce the risk of epilepsy in patients with febrile seizures.

Because of the benign nature of most febrile seizures, few children require drug treatment for these seizures. Counseling and educating parents and caregivers are important for the appropriate management of febrile seizures because they empower parents and alleviate the stress and fear that can negatively affect quality of life. In those cases in which treatment is indicated, treatment is focused on abortive therapy using benzodiazepines to prevent prolonged febrile seizures, as these seizures may be associated with the development of MTS and epilepsy. Overall, a better understanding of the natural history and outcomes of febrile seizures will aid physicians in educating parents and will help in avoiding unnecessary diagnostic and therapeutic interventions.

REFERENCES

1. Febrile seizures. *Consens Dev Conf Summ Natl Inst Health.* 1980;3:7-11.
2. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia.* 1993;34(4):592-596.
3. Shinnar S, Glauser TA. Febrile seizures. *J Child Neurol.* 2002;17(suppl 1):S44-S52.
4. Shinnar S. Febrile seizures. In: Swaiman KF, Ashwal S, Ferriero DM, eds. *Pediatric Neurology: Principles and Practice.* 4th ed. St Louis, MO: Mosby; 2006:1079-1090.
5. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. *N Engl J Med.* 1987;316(9):493-498.
6. Berg AT, Shinnar S, Hauser WA, et al. A prospective study of recurrent febrile seizures. *N Engl J Med.* 1992;327(16):1122-1127.
7. Berg AT, Shinnar S. Complex febrile seizures. *Epilepsia.* 1996;37(2):126-133.
8. Stafstrom CE. The incidence and prevalence of febrile seizures. In: Baram TZ, Shinnar S, eds. *Febrile Seizures.* San Diego, CA: Academic Press; 2002:1-25.
9. Dodson WE, DeLorenzo RJ, Pedley TA, Shinnar R, Treiman DM, Wannamaker BB. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. *JAMA.* 1993;270(7):854-859.
10. Maytal J, Shinnar S, Moshé SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. *Pediatrics.* 1989;83(3):323-331.
11. Shinnar S, Pellock JM, Moshé SL, et al. In whom does status epilepticus occur: age-related differences in children. *Epilepsia.* 1997;38(8):907-914.
12. Leung AK, Robson WL. Febrile seizures. *J Pediatr Health Care.* 2007;21(4):250-255.
13. Hauser WA. The prevalence and incidence of convulsive disorders in children. *Epilepsia.* 1994;35(suppl 2):S1-S6.
14. Sillanpää M, Camfield P, Camfield C, et al. Incidence of febrile seizures in Finland: prospective population-based study. *Pediatr Neurol.* 2008;38(6):391-394.
15. Vestergaard M, Pedersen CB, Sidenius P, Olsen J, Christensen J. The long-term risk of epilepsy after febrile seizures in susceptible subgroups. *Am J Epidemiol.* 2007;165(8):911-918.
16. Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: short-term outcome. *Neurology.* 1996;47(2):562-568.
17. Bethune P, Gordon K, Dooley J, Camfield C, Camfield P. Which child will have a febrile seizure? *Am J Dis Child.* 1993;147(1):35-39.
18. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, Hauser WA. Risk factors for a first febrile seizure: a matched case-control study. *Epilepsia.* 1995;36(4):334-341.
19. Theodore WH, Epstein L, Gaillard WD, Shinnar S, Wainwright MS, Jacobsen S. Human herpes virus 6B: possible role in epilepsy? *Epilepsia.* 2008;49(11):1828-1837.
20. Barone SR, Kaplan MH, Krilov LR. Human herpesvirus-6 infection in children with first febrile seizures. *J Pediatr.* 1995;127(1):95-97.
21. Suga S, Suzuki K, Ihira M, et al. Clinical characteristics of febrile convulsions during primary HHV-6 infection. *Arch Dis Child.* 2000;82(1):62-66.
22. Ward KN, Andrews NJ, Verity CM, Miller E, Ross EM. Human herpesviruses-6 and -7 each cause significant neurological morbidity in Britain and Ireland. *Arch Dis Child.* 2005;90(6):619-623.
23. Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. *N Engl J Med.* 1994;331(7):432-438.
24. Epstein LG, Nordli DR, Hamidullah A, et al. The role of primary human herpes virus 6, 7 (HHV-6, HHV-7) infection in febrile status epilepticus [abstract]. *Ann Neurol.* 2005;58(suppl 9):S79-S80.
25. Annegers JF, Blakley SA, Hauser WA, Kurland LT. Recurrence of febrile convulsions in a population-based cohort. *Epilepsy Res.* 1990;5(3):209-216.
26. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. *Pediatrics.* 1978;61(5):720-727.
27. Offringa M, Bossuyt PM, Lubsen J, et al. Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. *J Pediatr.* 1994;124(4):574-584.
28. Offringa M, Derksen-Lubsen G, Bossuyt PM, Lubsen J. Seizure recurrence after a first febrile seizure: a multivariate approach. *Dev Med Child Neurol.* 1992;34(1):15-24.
29. Knudsen FU. Recurrence risk after first febrile seizure and effect of short term diazepam prophylaxis. *Arch Dis Child.* 1985;60(11):1045-1049.
30. Berg AT, Shinnar S, Darefsky AS, et al. Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med.* 1997;151(4):371-378.
31. Pavlidou E, Tzitiridou M, Kontopoulos E, Panteliadis CP. Which factors determine febrile seizure recurrence? A prospective study. *Brain Dev.* 2008;30(1):7-13.
32. Shirts SB, Annegers JF, Hauser WA. The relation of age at first febrile seizure to recurrence of febrile seizures [abstract]. *Epilepsia.* 1987;28(5):625.
33. el-Radhi AS, Banajeh S. Effect of fever on recurrence rate of febrile convulsions. *Arch Dis Child.* 1989;64(6):869-870.
34. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. *N Engl J Med.* 1976;295(19):1029-1033.
35. Verity CM, Golding J. Risk of epilepsy after febrile convulsions: a national cohort study. *BMJ.* 1991;303(6814):1373-1376.
36. Knudsen FU, Paerregaard A, Andersen R, Andresen J. Long term outcome of prophylaxis for febrile convulsions. *Arch Dis Child.* 1996;74(1):13-18.
37. Annegers JF, Hauser WA, Elveback LR, Kurland LT. The risk of epilepsy following febrile convulsions. *Neurology.* 1979;29(3):297-303.
38. Camfield P, Camfield C, Gordon K, Dooley J. What types of epilepsy are preceded by febrile seizures? A population-based study of children. *Dev Med Child Neurol.* 1994;36(10):887-892.
39. Shinnar S. Febrile seizures and mesial temporal sclerosis. *Epilepsy Curr.* 2003;3(4):115-118.
40. Maytal J, Shinnar S. Febrile status epilepticus. *Pediatrics.* 1990;86(4):611-616.
41. Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. *Epilepsia.* 2000;41(4):412-420.
42. Chang YC, Guo NW, Wang ST, Huang CC, Tsai JJ. Working memory of school-aged children with a history of febrile convulsions: a population study. *Neurology.* 2001;57(1):37-42.
43. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. *N Engl J Med.* 1998;338(24):1723-1728.
44. Ellenberg JH, Nelson KB. Febrile seizures and later intellectual performance. *Arch Neurol.* 1978;35(1):17-21.
45. Verity CM, Ross EM, Golding J. Outcome of childhood status epilepticus and lengthy febrile convulsions: findings of national cohort study. *BMJ.* 1993;307(6898):225-228.

46. Shinnar S, Pellock JM, Berg AT, et al. Short-term outcomes of children with febrile status epilepticus. *Epilepsia*. 2001;42(1):47-53.
47. Tsuboi T. Genetic analysis of febrile convulsions: twin and family studies. *Hum Genet*. 1987;75(1):7-14.
48. Rich SS, Annegers JF, Hauser WA, Anderson VE. Complex segregation analysis of febrile convulsions. *Am J Hum Genet*. 1987;41(2):249-257.
49. Wallace RH, Wang DW, Singh R, et al. Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel beta1 subunit gene *SCN1B*. *Nat Genet*. 1998;19(4):366-370.
50. Nakayama J, Arinami T. Molecular genetics of febrile seizures. *Epilepsy Res*. 2006;70(suppl 1):S190-S198.
51. Audenaert D, Van Broeckhoven C, De Jonghe P. Genes and loci involved in febrile seizures and related epilepsy syndromes. *Hum Mutat*. 2006;27(5):391-401.
52. Audenaert D, Schwartz E, Claeys KG, et al. A novel *GABRG2* mutation associated with febrile seizures. *Neurology*. 2006;67(4):687-690.
53. Yu ZL, Jiang JM, Wu DH, et al. Febrile seizures are associated with mutation of seizure-related (*SEZ*) *6*, a brain-specific gene. *J Neurosci Res*. 2007;85(1):166-172.
54. Sun H, Zhang Y, Liang J, et al. *SCN1A, SCN1B,* and *GABRG2* gene mutation analysis in Chinese families with generalized epilepsy with febrile seizures plus. *J Hum Genet*. 2008;53(8):769-774.
55. Nabbout R, Prud'homme JF, Herman A, et al. A locus for simple pure febrile seizures maps to chromosome 6q22-q24. *Brain*. 2002;125(pt 12):2668-2680.
56. Kugler SL, Johnson WG. Genetics of the febrile seizure susceptibility trait. *Brain Dev*. 1998;20(5):265-274.
57. Hedera P, Ma S, Blair MA, et al. Identification of a novel locus for febrile seizures and epilepsy on chromosome 21q22. *Epilepsia*. 2006;47(10):1622-1628.
58. Nakayama J, Yamamoto N, Hamano K, et al. Linkage and association of febrile seizures to the *IMPA2* gene on human chromosome 18. *Neurology*. 2004;63(10): 1803-1807.
59. Practice parameter: the neurodiagnostic evaluation of the child with a first simple febrile seizure. American Academy of Pediatrics. Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures. *Pediatrics*. 1996;97(5):769-772; discussion 773-775.
60. Fetveit A. Assessment of febrile seizures in children. *Eur J Pediatr*. 2008;167(1):17-27.
61. Lorber J, Sunderland R. Lumbar puncture in children with convulsions associated with fever. *Lancet*. 1980;1(8172):785-786.
62. Shinnar S, Glauser T. Febrile seizures. In: Pellock JM, Bourgeois BF, Dodson WE, eds. *Pediatric Epilepsy: Diagnosis and Therapy.* 3rd ed. New York, NY: Demos Medical Publishing; 2008:293-301.
63. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. American Academy of Pediatrics. Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures. *Pediatrics*. 2008;121(6):1281-1286.
64. Kobayashi K, Ohtsuka Y, Ohmori I, et al. Clinical and electroencephalographic characteristics of children with febrile seizures plus. *Brain Dev*. 2004;26(4):262-268.
65. Maytal J, Steele R, Eviatar L, Novak G. The value of early postictal EEG in children with complex febrile seizures. *Epilepsia*. 2000;41(2):219-221.
66. VanLandingham KE, Heinz ER, Cavazos JE, Lewis DV. Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. *Ann Neurol*. 1998;43(4):413-426.
67. Lewis DV, Bello JA, Chan S, et al. FEBSTAT Study Team. Hippocampal abnormalities subsequent to febrile status epilepticus: findings on early postictal MRI imaging. *Epilepsia*. 2005;46(suppl 8):52-53.
68. Shinnar S. Prolonged febrile seizures and mesial temporal sclerosis. *Ann Neurol*. 1998;43(4):411-412.
69. Kondo K, Nagafuji H, Hata A, Tomomori C, Yamanishi K. Association of human herpesvirus 6 infection of the central nervous system with recurrence of febrile convulsions. *J Infect Dis*. 1993;167(5):1197-1200.
70. Berg AT. Are febrile seizures provoked by a rapid rise in temperature? *Am J Dis Child*. 1993;147(10):1101-1103.
71. Rantala H, Uhari M, Hietala J. Factors triggering the first febrile seizure. *Acta Paediatr*. 1995;84(4):407-410.
72. Dubé C, Vezzani A, Behrens M, Bartfai T, Baram TZ. Interleukin-1beta contributes to the generation of experimental febrile seizures. *Ann Neurol*. 2005;57(1):152-155.
73. Vezzani A, Moneta D, Richichi C, et al. Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. *Epilepsia*. 2002;43(suppl 5):30-35.
74. Gatti S, Vezzani A, Bartfai T. Mechanism of fever and febrile seizures: putative role of the interleukin-1 system. In: Baram TZ, Shinnar S, eds. *Febrile Seizures*. San Diego, CA: Academic Press; 2002:169-184.
75. Vezzani A, Baram TZ. New roles for interleukin-1 beta in the mechanisms of epilepsy. *Epilepsy Curr*. 2007;7(2):45-50.
76. Haspolat S, Mihci E, Coskun M, Gumuslu S, Ozben T, Yegin O. Interleukin-1beta, tumor necrosis factor-alpha, and nitrite levels in febrile seizures. *J Child Neurol*. 2002;17(10):749-751.
77. Dubé CM, Brewster AL, Richichi C, Zha Q, Baram TZ. Fever, febrile seizures and epilepsy. *Trends Neurosci*. 2007;30(10):490-496.
78. Baram TZ, Gerth A, Schultz L. Febrile seizures: an appropriate-aged model suitable for long-term studies. *Brain Res Dev Brain Res*. 1997;98(2):265-270.
79. Chen K, Baram TZ, Soltesz I. Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. *Nat Med*. 1999;5(8): 888-894.
80. Dubé C, Chen K, Eghbal-Ahmadi M, Brunson K, Soltesz I, Baram TZ. Prolonged febrile seizures in the immature rat model enhance hippocampal excitability long term. *Ann Neurol*. 2000;47(3):336-344.
81. Toth Z, Yan XX, Haftoglou S, Ribak CE, Baram TZ. Seizure-induced neuronal injury: vulnerability to febrile seizures in an immature rat model. *J Neurosci*. 1998;18(11):4285-4294.
82. Brewster A, Bender RA, Chen Y, Dubé C, Eghbal-Ahmadi M, Baram TZ. Developmental febrile seizures modulate hippocampal gene expression of hyperpolarization-activated channels in an isoform- and cell-specific manner. *J Neurosci*. 2002;22(11):4591-4599.
83. Poolos NP. The yin and yang of the h-channel and its role in epilepsy. *Epilepsy Curr*. 2004;4(1):3-6.
84. Santoro B, Baram TZ. The multiple personalities of h-channels. *Trends Neurosci*. 2003;26(10):550-554.
85. Chen K, Aradi I, Thon N, Eghbal-Ahmadi M, Baram TZ, Soltesz I. Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. *Nat Med*. 2001;7(3):331-337.
86. Germano IM, Zhang YF, Sperber EF, Moshe SL. Neuronal migration disorders increase susceptibility to hyperthermia-induced seizures in developing rats. *Epilepsia*. 1996;37(9):902-910.

87. Holtzman D, Obana K, Olson J. Hyperthermia-induced seizures in the rat pup: a model for febrile convulsions in children. *Science*. 1981;213(4511):1034-1036.
88. Tancredi V, D'Arcangelo G, Zona C, Siniscalchi A, Avoli M. Induction of epileptiform activity by temperature elevation in hippocampal slices from young rats: an in vitro model for febrile seizures? *Epilepsia*. 1992;33(2):228-234.
89. Berg AT, Shinnar S. Do seizures beget seizures? An assessment of the clinical evidence in humans. *J Clin Neurophysiol*. 1997;14(2):102-110.
90. Lynd-Balta E, Pilcher WH, Joseph SA. AMPA receptor alterations precede mossy fiber sprouting in young children with temporal lobe epilepsy. *Neuroscience*. 2004;126(1):105-114.
91. Cendes F. Febrile seizures and mesial temporal sclerosis. *Curr Opin Neurol*. 2004;17(2):161-164.
92. Maher J, McLachlan RS. Febrile convulsions. Is seizure duration the most important predictor of temporal lobe epilepsy? *Brain*. 1995;118(pt 6):1521-1528.
93. Scott RC, King MD, Gadian DG, Neville BG, Connelly A. Prolonged febrile seizures are associated with hippocampal vasogenic edema and developmental changes. *Epilepsia*. 2006;47(9):1493-1498.
94. Mathern GW, Pretorius JK, Babb TL. Influence of the type of initial precipitating injury and at what age it occurs on course and outcome in patients with temporal lobe seizures. *J Neurosurg*. 1995;82(2):220-227.
95. Mathern GW, Babb TL, Pretorius JK, Melendez M, Levesque MF. The pathophysiologic relationships between lesion pathology, intracranial ictal EEG onsets, and hippocampal neuron losses in temporal lobe epilepsy. *Epilepsy Res*. 1995;21(2):133-147.
96. Shinnar S, Hesdorffer DC, Nordli DRJ, et al. Phenomenology of prolonged febrile seizures: results of the FEBSTAT study. *Neurology*. 2008;71(3):170-176.
97. Knudsen FU. Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. *Arch Dis Child*. 1979;54(11):855-857.
98. Dieckmann RA. Rectal diazepam for prehospital pediatric status epilepticus. *Ann Emerg Med*. 1994;23(2):216-224.
99. Camfield CS, Camfield PR, Smith E, Dooley JM. Home use of rectal diazepam to prevent status epilepticus in children with convulsive disorders. *J Child Neurol*. 1989;4(2):125-126.
100. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ*. 2000;321(7253):83-86.
101. Mahmoudian T, Zadeh MM. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav*. 2004;5(2):253-255.
102. McIntyre J, Robertson S, Norris E, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet*. 2005;366(9481):205-210.
103. O'Dell C, Shinnar S, Ballaban-Gil KR, et al. Rectal diazepam gel in the home management of seizures in children. *Pediatr Neurol*. 2005;33(3):166-172.
104. Knudsen FU. Febrile seizures: treatment and prognosis. Epilepsia. 2000;41(1):2-9.
105. Fişgin T, Gurer Y, Tezic T, et al. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study. *J Child Neurol*. 2002;17(2):123-126.
106. Jeannet PY, Roulet E, Maeder-Ingvar M, Gehri M, Jutzi A, Deonna T. Home and hospital treatment of acute seizures in children with nasal midazolam. *Eur J Paediatr Neurol*. 1999;3(2):73-77.
107. Cloyd JC, Lalonde RL, Beniak TE, Novack GD. A single-blind, crossover comparison of the pharmacokinetics and cognitive effects of a new diazepam rectal gel with intravenous diazepam. *Epilepsia*. 1998;39(5):520-526.
108. Verrotti A, Latini G, di Corcia G, et al. Intermittent oral diazepam prophylaxis in febrile convulsions: its effectiveness for febrile seizure recurrence. *Eur J Paediatr Neurol*. 2004;8(3):131-134.
109. Pellock JM, Shinnar S. Respiratory adverse events associated with diazepam rectal gel. *Neurology*. 2005;64(10):1768-1770.
110. O'Dell C. What do we tell parents of a child with simple or complex febrile seizures? In: Baram TZ, Shinnar S, eds. *Febrile Seizures*. San Diego, CA: Academic Press; 2002:305-316.
111. Knudsen FU. Practical management approaches to simple and complex febrile seizures. In: Baram TZ, Shinnar S, eds. *Febrile Seizures*. San Diego, CA: Academic Press; 2002:273-304.
112. Rossi LN, Rossi G, Bossi A, Cortinovis I, Brunelli G. Behaviour and confidence of parents instructed in home management of febrile seizures by rectal diazepam. *Helv Paediatr Acta*. 1989;43(4):273-281.
113. Camfield PR, Camfield CS, Shapiro SH, Cummings C. The first febrile seizure--antipyretic instruction plus either phenobarbital or placebo to prevent recurrence. *J Pediatr.* 1980;97(1):16-21.
114. Rutter N, Metcalfe DH. Febrile convulsions--what do parents do? *Br Med J*. 1978;2(6148):1345-1346.
115. Baumann RJ. Technical report: treatment of the child with simple febrile seizures. *Pediatrics*. 1999;103(6):e86.
116. Knudsen FU, Vestermark S. Prophylactic diazepam or phenobarbitone in febrile convulsions: a prospective, controlled study. *Arch Dis Child*. 1978;53(8):660-663.
117. Knudsen FU. Effective short-term diazepam prophylaxis in febrile convulsions. *J Pediatr*. 1985;106(3):487-490.
118. Pavlidou E, Tzitiridou M, Panteliadis C. Effectiveness of intermittent diazepam prophylaxis in febrile seizures: long-term prospective controlled study. *J Child Neurol*. 2006;21(12):1036-1040.
119. Rosman NP, Colton T, Labazzo J, et al. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med*. 1993;329(2):79-84.
120. Wolf SM, Carr A, Davis DC, et al. The value of phenobarbital in the child who has had a single febrile seizure: a controlled prospective study. *Pediatrics*. 1977;59(3):378-385.
121. Wallace SJ, Smith JA. Successful prophylaxis against febrile convulsions with valproic acid or phenobarbitone. *Br Med J*. 1980;280(6211):353-354.
122. Antony JH, Hawke SH. Phenobarbital compared with carbamazepine in prevention of recurrent febrile convulsions. A double-blind study. *Am J Dis Child*. 1983;137(9):892-895.
123. Mamelle N, Mamelle JC, Plasse JC, Revol M, Gilly R. Prevention of recurrent febrile convulsions--a randomized therapeutic assay: sodium valproate, phenobarbital and placebo. *Neuropediatrics*. 1984;15(1):37-42.
124. Bacon CJ, Hierons AM, Mucklow JC, Webb JK, Rawlins MD, Weightman D. Placebo-controlled study of phenobarbitone and phenytoin in the prophylaxis of febrile convulsions. *Lancet*. 1981;2(8247):600-604.

125. Lee K, Melchior JC. Sodium valproate versus phenobarbital in the prophylactic treatment of febrile convulsions in childhood. *Eur J Pediatr*. 1981;137(2):151-153.
126. Camfield PR, Camfield CS, Tibbles JA. Carbamazepine does not prevent febrile seizures in phenobarbital failures. *Neurology*. 1982;32(3):288-289.
127. Ngwane E, Bower B. Continuous sodium valproate or phenobarbitone in the prevention of 'simple' febrile convulsions. Comparison by a double-blind trial. *Arch Dis Child*. 1980;55(3):171-174.
128. Dreifuss FE, Rosman NP, Cloyd JC, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med*. 1998;338(26):1869-1875.
129. Wolf SM, Forsythe A. Epilepsy and mental retardation following febrile seizures in childhood. *Acta Paediatr Scand*. 1989;78(2):291-295.
130. Shinnar S, Berg AT. Does antiepileptic drug therapy prevent the development of "chronic" epilepsy? *Epilepsia*. 1996;37(8):701-708.
131. Rosman NP, Labazzo JL, Colton T. Factors predisposing to afebrile seizures after febrile convulsions and preventive treatment [abstract]. *Ann Neurol*. 1993;34:452.
132. Baumer JH, David TJ, Valentine SJ, Roberts JE, Hughes BR. Many parents think their child is dying when having a first febrile convulsion. *Dev Med Child Neurol*. 1981;23(4):462-464.
133. Gordon KE, Dooley JM, Camfield PR, Camfield CS, MacSween J. Treatment of febrile seizures: the influence of treatment efficacy and side-effect profile on value to parents. *Pediatrics*. 2001;108(5):1080-1088.