Review: Fever Associated Seizures
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Introduction

Febrile seizures are the most common cause of seizures in childhood. They occur in 2 to 4 percent of children younger than five years of age in most populations. Racial and geographic variations may be important leading to a higher incidence in some groups like Japan and the developing countries.

Definition

Febrile seizure is defined as a seizure in neurologically healthy infants and children between 6 months and 6 years of age, associated with fever >38°C or higher and without any evidence of intracranial infection or inflammation or acute systemic metabolic abnormality as a defined cause and with no history of previous afebrile seizures.\(^{(1,2)}\) Generally, febrile seizures occur during early phase of rising temperature and are uncommon after 24 hours of onset of fever.\(^{(3,4,5)}\)

Classification

Febrile convulsions are categorized into two categories, simple (benign), or complex, based upon clinical features.

Simple febrile seizures are the most common and are characterized by seizures that are primarily generalized, usually tonic then clonic, associated with fever, last less than 15 minutes, and do not recur within a 24 hour period.\(^{(1,6)}\) The child is otherwise neurologically healthy without any neurological abnormality on examination or by developmental history. Fever and seizure should not be caused by any intracranial infection or inflammation and there are no postictal neurological abnormalities.

Complex febrile seizures are characterized by episodes that have focal features or postictal paresis, and occur in a series with a total duration greater than 10-15 minutes.\(^{(2,7,8,9,16)}\) Seizures recur within 24 hours or within the same febrile illness and may be associated with postictal neurological abnormalities like Todd’s paresis.

There is another category called symptomatic febrile seizures in which the child has a preexisting neurological abnormality or an acute illness.

Febrile Status Epilepticus is a febrile seizure lasting > 30 minutes by traditional definition but any child with a seizure for more than 5 minutes or a child who is brought to hospital with seizures is treated as a Febrile Status Epilepticus.\(^{(7)}\)

Incidence

Febrile seizures occur in 2-5 % of children under the age of 5 years.\(^{(10,11,12)}\) The median age of occurrence is 18-22 months.\(^{(8,12,13,14)}\) Studies from Western Europe and the USA report an incidence of 2–5%. The incidence elsewhere in the world varies between 5–10% (India), 8.8% (Japan), and 14% (Guam).\(^{(14)}\) The incidence of
complex febrile seizures varies from 9-35 %.\textsuperscript{(16,17)} It may be important to establish this at presentation because children with prolonged or multiple FS are at an increased risk of developing unprovoked seizures. Febrile Status Epilepticus accounts for 25% of all episodes of status epilepticus in children.\textsuperscript{(18)}

**Etiology and Pathophysiology**

This is a unique disorder that occurs in early childhood and only in association with an elevation of temperature. Febrile seizures are an extremely heterogeneous condition with a complicated and, as yet, unclear pathophysiological and genetic basis.

It may be that fever-induced factors (e.g., interleukin-1beta) are proconvulsant in individuals who are susceptible based upon the stage of brain development and genetic susceptibility.\textsuperscript{(19,20)} Certain ion channels in the brain are temperature sensitive and may generate fever-associated synchronized neuronal activity.\textsuperscript{(21,22)}

**Predisposing factors**

Susceptibility to febrile seizures has been linked with abnormalities in neurotransmitters. However, whether observed abnormalities were primary events or were secondary to the convulsions is unclear. CSF neopterin concentrations may be raised in children with febrile seizures. This finding may suggest immune activation within the central nervous system as neopterin is secreted by activated macrophages.\textsuperscript{(23)} CSF concentration of gamma-aminobutyric acid (GABA), an inhibitory transmitter, was seen in samples obtained after the seizure in certain studies.\textsuperscript{(24)} However, the samples were obtained after the convulsion and, thus, may be the effect rather than the cause of the seizure. The same findings of low CSF GABA was not confirmed in other studies of children with febrile seizures.\textsuperscript{(25)}

**Infections** - Febrile seizures can occur during both viral and bacterial infections. Seizures can happen with any condition that causes a fever, including common childhood illnesses like respiratory tract illnesses, influenza A\textsuperscript{(26)}, otitis media, shigella or roseola caused by herpesvirus 6.\textsuperscript{(27,28)}

**Immunizations** - The risk of febrile seizures is increased after administration of diphtheria, tetanus toxoid, and whole-cell pertussis (DTP)\textsuperscript{(29,30)} and measles, mumps, and rubella (MMR) vaccine.\textsuperscript{(31,32)} Studies by Barlow and associates (2001) and Walker and colleagues (1988) found a 4-fold increase in the risk of febrile seizures within 1-3 days of receipt of DTP vaccination. With regard to MMR vaccination, the risk of febrile seizures increases by 1.5 and 3.0 fold, with the peak occurring 1-2 weeks after vaccination; an additional 25-34 febrile seizures have been estimated to occur per 1,00,000 doses of MMR administered. In a large cohort study, febrile
seizures were significantly increased on the day of DTP vaccination and 8 to 14 days following MMR vaccination.\textsuperscript{30,32} The risk for subsequent seizures or neurodevelopmental disabilities was comparable in children with febrile seizures whether or not they were associated with vaccination. Because vaccines can cause fever, febrile seizures sometimes happen after vaccination, although rarely. Medicines, such as acetaminophen and ibuprofen, can lower fevers in children. However, scientific studies have not shown that these fever-reducing medicines will prevent febrile seizures in children. Aspirin and aspirin-containing products should not be used to reduce fever in children because of the increased risk for syndrome with aspirin ingestion and viral infections.

<table>
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<th>Table 1 : Factors predisposing to febrile seizures</th>
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<tr>
<td>• Infections - both viral and bacterial</td>
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<td>• Immunization - DTP and MMR</td>
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<tr>
<td>• Iron deficiency</td>
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<tr>
<td>• Genetic susceptibility</td>
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<tr>
<td>• Obstetric complications like difficult birth, neonatal asphyxia and coiling of umbilical cord</td>
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\textbf{Iron deficiency} may play a role in the pathogenesis. Certain studies have shown significantly lower levels of mean ferritin levels in children with a first febrile seizure than in matched controls with febrile illness but no convulsions.\textsuperscript{34,35} Other exogenous circumstances that have been identified as predicting an increased risk of initial febrile seizures include difficult birth, neonatal asphyxia, and coiling of the umbilical cord.\textsuperscript{36} Children with febrile seizures and the exogenous conditions previously listed are likely to have affected family members, and have a risk of recurrence of seizures on $\geq 5$ occasions.

\textbf{Genetic susceptibility} - Genetic and familial factors appear to be important factors in the expression of febrile convulsions and the subsequent development of epilepsy in some children. The risk of developing FS is higher in some families than in others.\textsuperscript{36,37,38,39} A positive family history for FS can be elicited in 25–40% of patients with febrile seizures and the reported frequency in siblings of children with FS ranges from 9% to 22%.\textsuperscript{40} Monozygotic twins have a much higher concordance rate than do dizygotic twins, in whom the rate is similar to that of other siblings. In many families the disorder is inherited as an autosomal dominant trait. Susceptibility to febrile seizures has been linked to several genetic loci in different families. Identified single genes include FEB 1,2,3,4,5,6, and 7 genes on chromosomes 8q13-q21\textsuperscript{41}, 19p13.3\textsuperscript{42}, 2q24\textsuperscript{43}, 5q14-q15\textsuperscript{44}, 6q22-24\textsuperscript{45}, 18p11.2\textsuperscript{46} and 21q22\textsuperscript{47}. Only the function of FEB 2 is known: it is a sodium channel gene, SCN1A. One study suggests that common polymorphism in a sodium channel gene (splice site variant SCN1A) is a common risk factor for febrile seizures.\textsuperscript{48} Any type of epilepsy can be preceded by febrile seizures.
A few epilepsy syndromes typically start with febrile seizures. GEFS+ is a syndromic autosomal dominant disorder where afflicted individuals can exhibit numerous epilepsy phenotypes. GEFS+ can persist beyond early childhood (i.e., 6 years of age). GEFS+ is also now believed to encompass three other epilepsy disorders: severe myoclonic epilepsy of infancy (SMEI), which is also known as Dravet's syndrome, borderline SMEI (SMEB), and intractable epilepsy of childhood (IEC). There are at least six types of GEFS+, delineated by their causative gene. Known causative genes are the sodium channel α subunit genes SCN1A, an associated α subunit SCN1B, and a GABAA receptor α subunit gene, GABRG2 and there is another gene related with calcium channel the PCDH19 which is also known as Epilepsy Female with Mental Retardation. Penetration for this disorder is estimated at approximately 60%. Individuals with GEFS+ present with a range of epilepsy phenotypes. These include febrile seizures that end by age 6 (FS), such seizures extending beyond age 6 that may include afebrile tonic-clonic, myoclonic, absence, atonic seizures and myoclonic-astatic epilepsy. Individuals may also present with SMEI, which is characterized by generally tonic-clonic seizures, impaired psychomotor development, myoclonic seizures, ataxia, and poor response to many epileptic drugs.

Dravet syndrome is considered to be the most severe phenotypic spectrum of febrile seizures plus. It's onset is in the first year of life, characterized by febrile and afebrile unilateral clonic seizures recurring every 1 or 2 months. These seizures are typically induced by fever, but they are more prolonged, more frequent, and come in clusters. Seizures subsequently occur with lower fevers and then without fever. During the second year of life, myoclonus, atypical absences, and partial seizures occur frequently and developmental delay follows. This syndrome is usually caused by a new mutation; the mutated gene is located on 2q24-31 and encodes for SCN1A, the same gene mutated in GEFS+ spectrum. However, in Dravet syndrome the mutations lead to loss of function and thus to a more severe phenotype. The majority of patients who had prolonged febrile seizures and encephalopathy after vaccination and who had been presumed to have suffered from vaccine encephalopathy have Dravet syndrome mutations, indicating that their disease is due to the mutation and not secondary to the vaccine.

Febrile seizures and temporal lobe epilepsy - This remains one of the most controversial issues in epilepsy. Retrospective studies from tertiary centers report that as many as 40% of adults with intractable temporal lobe epilepsy give a history of complex (specifically prolonged) FS in childhood. Another study found a strong association between prolonged and focal FS and the development of TLE. These findings are supported by magnetic resonance imaging (MRI) studies showing hippocampal sclerosis and atrophy in patients who experienced prolonged FS in childhood. The selection of children and the timing of neuroimaging have varied between studies, making evaluation of any potential evolving process difficult. A specific study employing MRI as a research tool, that was undertaken within 48
hours of a prolonged FS (including febrile status epilepticus), showed evidence of temporal lobe (hippocampal) edema. Subsequent follow up imaging within 12 months in this population showed resolution of the edema and did not show any hippocampal atrophy or mesial temporal sclerosis (MTS) in the previously swollen temporal lobes. The identification of hippocampal atrophy in patients with a previous history of prolonged FS does not necessarily prove a causal relation as seen in certain studies where patients with hippocampal atrophy and MTS had no history of FS.

Current opinion supports an association between prolonged FS and pre-existing lesions within the temporal lobe—and that this may subsequently facilitate the development of hippocampal atrophy. In addition, the contradictory findings obtained from epidemiological, neuroimaging, and pathological studies would also suggest that the association of complex FS with hippocampal atrophy and TLE reflects complex interactions with genetic or environmental factors (or both), which may subsequently facilitate the development of TLE. This increased susceptibility is likely to be multifactorial but may involve cytokines, and specifically interleukin-1.

**Clinical features**

A careful history and a thorough general and neurological examination is the cornerstone of an accurate diagnosis. A detailed account of the child's behavior preceding, during, and following a "spell" is critical. Confirm that the child has had a seizure. Determining the time of day and the activity in which the child was engaged prior to the seizure is important. The physician needs to confirm if the seizure occurred only with illness and documented fever or it was provoked (e.g. head injury) or there were any other acute medical events. Try to localize the infection. Children with a febrile seizure are neurologically and developmentally normal before and after the episode. Rule out any possibility of meningitis, encephalitis or encephalopathy. A detailed history including family history of FS, epilepsy, and sudden deaths in the family is mandatory.

Febrile seizures occur in children between the ages of six months and six years, with the majority occurring in children between 12 to 18 months of age. Febrile seizures have been reported in children over six years of age, but in older children, febrile seizures should be considered a diagnosis of exclusion.

The majority of children have their febrile seizures on the first day of illness and, in some cases, it is the first manifestation that the child is ill. The degree of fever associated with febrile convulsions is variable, and approximately 25 percent of events occur when the temperature is between 38°C and 39°C.

**Majority of children have their febrile seizures on the first day of illness**
They are often seen as the temperature is increasing rapidly but may develop as the fever is declining. Recurrent febrile seizures do not necessarily occur with the same degree of fever as the first episode and do not occur every time the child has a fever.

Simple febrile seizures are the most common type encountered in children. Generalized seizures are mainly clonic, but other forms include atonic and tonic spells. The facial and respiratory muscles are commonly involved.

Complex febrile seizures (focal features, seizures longer than 15 minutes or multiple episodes within 24 hours) are unusual; prolonged convulsions occur in fewer than 10 percent and focal features in fewer than 5 percent of children with febrile seizures. An initial simple febrile seizure may be followed by complex seizures, but the majority of children who develop complex febrile seizures do so with their first seizure.

Some patients present in febrile status epilepticus, i.e. continuous seizures or intermittent seizures without neurologic recovery, either lasting for a period of 30 minutes or longer.

Physical examination findings reveal a neurologically and developmentally healthy child. It is especially important that the child should have no signs of meningitis or encephalitis (e.g., stiff neck or persistent mental status changes).

**Findings which suggest another diagnosis**

The physician should look for congenital ocular defects, the retinal changes associated with certain neurocutaneous and neurodegenerative disorders, or signs of an earlier infection. The abdominal examination may reveal hepatosplenomegaly, suggesting a storage disease. A cardiac examination, including an ECG, is necessary if concern exists about a cardiogenic cause for the patient's episodes. Episodes of disturbed neurologic function caused by decreased cardiac output (e.g., prolonged QT syndrome or pulmonary hypertension) may closely mimic complex partial seizures, including the presence of an aura. Dysmorphic features and other congenital anomalies, body asymmetries, and unusual skull shapes should be noted. The skin examination is of particular importance in the evaluation of children with seizures as many neurocutaneous disorders are associated with epilepsy. The cutaneous features of tuberous sclerosis like ash leaf spots, the facial angiomata of Sturge-Weber syndrome, the cafe au lait spots of neurofibromatosis, the nevi of linear nevus syndrome and the swirling hypopigmentation of Ito syndrome are all characteristic physical findings.

**Differential Diagnosis**

Involuntary movements can occur in sick children and be confused with seizures. Rigors can usually be distinguished from seizures. Rigors are common and are characterized by fine rhythmic oscillatory movements about a joint. They rarely involve facial or respiratory muscles, which frequently occur during febrile seizures. In addition, rigors usually involve both sides of the body simultaneously and are not associated with loss of consciousness, in contrast to children with generalized
seizures. Thus, bilateral manifestations without apparent unconsciousness strongly suggest that the movements are not convulsive.

Meningitis and Encephalitis are the main concerns in a child presenting with fever and seizures. A thorough evaluation by an experienced clinician almost always will detect the child with meningitis. Children with status epilepticus (SE) and fever are more likely to have bacterial meningitis than those with a short seizure. Meningitis must be considered as a diagnostic possibility in children with SE and fever.

An underlying metabolic disorder presenting as a seizure in a febrile child is rare. Infants with a history of vomiting, diarrhea, and altered fluid intake may have electrolyte abnormalities (e.g. hypernatremia, hyponatremia) that can lead to seizures. Rarely, a febrile seizure may be the first sign of a metabolic disease (e.g. a mitochondrial cytopathy including “Leigh’s syndrome” or progressive neuronal degeneration of childhood), an inflammatory disorder (e.g. Rasmussen’s encephalitis), or one of the more malignant epilepsy syndromes (e.g. severe myoclonic epilepsy in infancy). The possibility of a metabolic disorder may be suggested from the history and examination (e.g. developmental regression, family history of sudden death in infancy/childhood, failure to thrive, hepatosplenomegaly, micro- and macrocephaly).

**Diagnostic tests**

Diagnostic testing is not necessary in most patients with simple febrile seizures. Physician should focus on diagnosing the cause of fever and ruling out meningitis.

A complete blood count and measurement of serum electrolytes, blood sugar, calcium, phosphorus, magnesium and urea nitrogen should be measured only when the patient has a history of vomiting, diarrhea, and abnormal fluid intake, or when physical findings of dehydration or edema exist.

**Lumbar puncture**

It is clearly important to consider and, where appropriate, exclude meningitis or encephalitis in any child who presents with FS. The estimated incidence of meningitis in children who present with an apparent FS is 2–5%. The yield of positive findings from LP varies between studies, and is generally low in the absence of risk factors including focal seizures, and suspicious clinical findings. The American Academy of Pediatrics (AAP) recommends Lumbar Puncture in the setting of febrile seizures in clinically suspected cases of meningitis or intracranial infection. LP should be considered in infants between 6 and 12 months if the immunization status for Haemophilus influenzae type B or Streptococcus
Pneumoniae is deficient or undetermined. LP should be considered when the patient is on antibiotics because antibiotic treatment can mask the signs and symptoms of meningitis. Seizures are the major sign of meningitis in 13-15% of children presenting with this disease, and 30-35% of children have no other meningeal signs. The AAP strongly recommends LP in patients under 12 months of age presenting with fever and seizure because meningeal signs may be minimal or absent in this age group. (67,68,74,75) LP is to be considered in patients 12 to 18 months of age as symptoms and signs of meningitis may be subtle. (67,74,75) For children > 18 months, a lumbar puncture is indicated in the presence of clinical signs and symptoms of meningitis (e.g. neck stiffness, Kernig's sign, Brudzinski's sign) or if the history and/or examination suggest an intracranial infection.

LP should also be considered when febrile seizures occur after the second day of illness, or when, based on history or examination, the clinician remains concerned about possible central nervous system infection. Febrile status epilepticus may be another possible indication for lumbar puncture. (76-78) For the well-appearing child after a febrile seizure, the yield of lumbar puncture is very low. CSF pleocytosis in a child with a febrile seizure should be considered as a sign of infection until proved otherwise, indicating further evaluation. Blood glucose and blood culture should be performed concurrently.

**Imaging**

Neuroimaging with computed tomography (CT) or MRI is not required for children with simple febrile seizures. (75,78,79) Neuroimaging is indicated in children with abnormally large heads, a persistently abnormal neurologic examination, particularly with focal features, or signs and symptoms of increased intracranial pressure. (78,79) According to AAP practice parameter, a CT or MRI is not recommended in evaluating the child after a first simple febrile seizure. Patients with febrile status epilepticus may be candidates for neuroimaging, because they may be at risk for later temporal epilepsy. (67,75-78) These patients have been reported to have swelling of their hippocampus acutely and subsequent long term hippocampal atrophy. Magnetic resonance imaging is superior to computerized tomography (CT), specifically for those situations where there may be an underlying inflammatory (e.g.; herpes simplex or Rasmussen’s encephalitis) or structural (e.g.; cerebral dysgenesis, tumours, and vascular malformations) cause.

**EEG**

Routine electroencephalography (EEG) is not warranted, particularly in the setting of a neurologically healthy child with a simple partial febrile seizure. Abnormalities are more likely to be found when the test is performed shortly after the seizure and
when convulsions are of long duration and have focal features. Published studies demonstrate that the vast majority of these children have a normal EEG. In addition, some of those with an abnormal EEG have remained free of seizures for the duration of their follow-up. On the other hand, some of the children with a normal initial EEG have experienced 1 or more afebrile seizures subsequent to the EEG. An EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal.\textsuperscript{[83,84]} Finally, no evidence indicates that beginning anticonvulsant therapy for a child with simple febrile seizures and an abnormal EEG will alter the child's eventual outcome. EEG's performed within 2 weeks of a febrile seizure often have nonspecific slowing, usually posteriorly. Thus, in many cases, if an EEG is indicated, it should be delayed until or repeated after > 2 weeks have passed. At times, if the patient does not recover immediately from a seizure, then EEG can help distinguish between ongoing seizure activity and a prolonged postictal period sometimes termed a nonepileptic twilight state (NETS).\textsuperscript{[1]} If an EEG is done, it should be performed for at least 30 minutes in wakefulness and in sleep according to international guidelines. EEG should therefore be restricted to special cases in which epilepsy is highly suspected, and it should be done to delineate the type of epilepsy rather than to predict its occurrence.

**Treatment**

**General management**

Airway, respiratory status, and circulatory status are continuously assessed in patients with active seizures. Place the child in a semi prone position to minimize the risk of aspiration. Blood should be obtained for electrolytes and glucose determination, if indicated.

**Antiepileptic drugs**

Antiepileptic drugs should be administered intravenously, if possible, starting with a benzodiazepine such as Lorazepam (0.05 to 0.1 mg/kg), Diazepam (0.2 – 0.5 mg/kg) or Midazolam (0.2 mg/kg). Lorazepam appears to be as effective as Diazepam in seizure control and has a more protracted duration of action and fewer side effects.\textsuperscript{[83]} If intravenous access is not available, buccal midazolam (0.2 -0.5 mg/kg) or intranasal lorazepam (0.1 mg/kg) are effective options. Rectal diazepam (0.2 mg/kg in > 12 year olds - 0.5 mg/kg in 2-5 year olds) has also been found to be safe and effective. It is completely absorbed and anticonvulsant plasma concentrations are obtained within 2-4 min., almost as rapidly as an intravenous dose.\textsuperscript{[84]} Studies have shown that midazolam (0.2 -0.3 mg/kg) given intranasally is as
safe and as effective as diazepam given intravenously in the management of febrile seizures in children. Rectal diazepam remains first-line therapy for emergency treatment of prolonged or closely-clustered seizures in settings where intravenous access is not readily available. Buccal midazolam appears to be more effective than rectal, and is suggested as primary hospital emergency department treatment of prolonged seizures prior to establishment of intravenous access. Intramuscular and intranasal administration of midazolam appears to have similar efficacy as rectal diazepam. If the seizure persists, an additional dose may be given. The child's respiratory status needs to be monitored carefully and intubation undertaken if the ventilatory status becomes inadequate.

Persistence of the seizure is rare. When it does, the child can be treated with fosphenytoin (15 to 20 PE/kg), intravenous phenobarbitone (5-20 mg/kg loading), phenytoin (15-20 mg/kg loading) or valproate (25 mg/kg loading). Precautions about the rate of infusion of fosphenytoin and phenytoin and the other medications need to be followed because side effects often depend on the infusion rate.

The fever should be treated as the seizures are controlled. Antipyretics are not effective in preventing recurrent febrile seizures, but are useful in making the child more comfortable.

Most children should be observed until they are awake and alert. The decision to hospitalized the child should be individualized. Children, especially those with a first febrile seizure, should be hospitalized if any of the following are present: lethargy beyond postictal stage; unstable clinical status; age <18 months; complex features; uncertain home situation; unclear follow up. It must be remembered that a history of previous febrile convulsion does not rule out possibility of meningitis. Any child with the slightest suspicion of meningitis should be admitted and investigated.

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<thead>
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<th>Table 2: Need for hospitalization in febrile seizures</th>
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<tr>
<td>• Lethargy beyond postictal stage</td>
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<td>• Unstable clinical status</td>
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<tr>
<td>• Age - less than 18 months</td>
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<tr>
<td>• Complex features</td>
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<tr>
<td>• Suspicion of meningitis</td>
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<tr>
<td>• Uncertain home situation</td>
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<tr>
<td>• Unclear follow-up</td>
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**Long term treatment**

Antiepileptic therapy — Children with febrile seizures are at increased risk for recurrent febrile as well as the development of afebrile seizures, suggesting a role for prophylactic treatment with chronic antiepileptic medications (AEDs). However, given the benign nature of recurrent febrile seizures, there is increasing consensus that risks of AED treatment outweigh potential benefits for most patients. There is no
available evidence that the use of chronic AEDs or the prevention of recurrent febrile seizures is associated with a reduced risk of epilepsy. Valproate and Phenobarbital are effective in preventing the recurrence of simple febrile seizures. In a controlled double blind study, daily therapy with Phenobarbital reduced the rate of subsequent febrile seizure from 25 per 100 subjects/year to 5 per 100 subjects/year. (99, 100) The adverse effects include behavioral problems such as hyperactivity and hyper-sensitivity reactions. Long-term phenobarbital treatment appears to influence cognition and behavior, a large price for prevention of a benign condition. Valproate is as effective as phenobarbitone in preventing recurrent, simple febrile seizures. In randomized, controlled studies, only 4% of children taking valproate as opposed to 35% of control subjects had a subsequent febrile seizure. (99) Drawbacks to therapy with valproate include its rare association with fatal hepatotoxicity, thrombocytopenia, weight loss and gain, gastrointestinal disturbances and pancreatitis.

Diazepam administered intermittently either rectally as suppositories, or solution or orally at the onset of fever has been shown to be effective in preventing recurrence of febrile seizures. (92-95) A dose of 0.3 to 0.5 mg/kg (max 10 mg) is used and repeated every 8-12 hours if temperature is 38°C or more. A maximum of 4-5 doses are given per illness. Intermittent clonazepam (1mg/kg/day) given orally has also been found to be useful in preventing febrile seizure recurrences. (96) A potential drawback to intermittent medication is that seizure could occur before fever is noticed. Adverse effects of oral diazepam include lethargy, drowsiness and ataxia. The sedation associated with this therapy could mask evolving signs of meningitis. It must however be remembered that this therapy does not decrease the incidence of later epilepsy in children with febrile seizures.

The AAP recommends that "Based on the risk and benefits of effective therapies, neither continuous nor intermittent anticonvulsant therapy is recommended for children with one or more simple febrile seizures. The American Academy of Pediatrics recognizes that recurrent episodes of febrile seizures can create anxiety in some parents and their children and as such appropriate educational and emotional support should be provided" (95)

There is no data upon which to base a recommendation regarding AED prophylaxis in children with complex febrile seizures. Treatment in such cases is individualized based upon underlying risk factors, but there is no evidence that supports treatment in any one subset of patients.

For children who have had febrile seizures, treatment with antipyretics at the time of
a febrile illness may be helpful in overall management but does not appear to affect the recurrence rate of febrile seizures.

Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy and educated on how to handle a seizure acutely. They should be told that febrile seizures are common, that recurrences are unlikely, and that the risk of brain damage and subsequent epilepsy are rare. They should be taught how to provide first aid in case of a seizure and what to do if their child has a febrile illness and fever management. If the parents are very anxious concerning their child’s seizures, intermittent oral diazepam (0.3 mg/kg every 8 hours), clonazepam (0.1 mg/kg/day), clobazam (1 mg/kg/day) or nitrazepam can be given during febrile illnesses. Other therapies have included intermittent diazepam prophylaxis (0.5 mg/kg as a rectal suppository every 8 hours), Phenobarbital (4-5 mg/kg/day in 1-2 divided doses) and valproate (20-30 mg/kg/day in 2-3 divided doses).

Children and Adults with Dravet syndrome experience multiple seizure types that are resistant to most anti-epileptic medications. Currently, the evidence supports the use of “rational polytherapy” which consists of a step-wise introduction of medications that have been shown to improve seizure control in patients with Dravet syndrome until the patient either responds favorably or experiences unacceptable side effects. The following medications have been shown to benefit patients with Dravet syndrome: divalproex sodium and derivatives, topiramate, stiripentol, clobazam, clonazepam, levetiracetam, bromides. Non-pharmacologic therapy with the ketogenic diet has been shown to improve seizure control in a significant percentage of children with Dravet syndrome. Focal resective surgery is usually not helpful as SMEI is a systemic disorder without identifiable focal pathology.

It should also be noted that the following medications may aggravate seizures in Dravet syndrome: lamotrigine, phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, and vigabatrin.

Risk factors for recurrence

Most children with FS do not experience further FS, but one third will; age would appear to be the single, strongest, and most consistent risk factor. More than half of the subsequent febrile seizures occur during the first year after the initial FS and over 90% recur within two years. Of those who experience a second febrile seizure, the risk of recurrence increases 2-fold. A family history of febrile seizures (but not epilepsy) in a first degree relative, is associated with an increased risk of recurrence. Recurrences appear to be more likely in children whose initial FS occurred with a relatively low fever, when multiple initial seizures occurred during the same febrile episode, and when the first febrile seizure was prolonged. However, febrile status epilepticus in an otherwise normal child does not appear to significantly increase the risk for further febrile seizures or the development of epilepsy. Age of onset is perhaps the single strongest and most consistent predictor
of recurrent febrile seizures: the younger the child, the greater the risk (50% in <1 year old versus 20% in >3 years old).

The most crucial risk factors for febrile status include young age at onset, family history of unprovoked seizure and an initial partial febrile seizure. Risk factors for the first febrile seizure comprise the height of the temperature and family history of febrile seizure.

### Table 3: Risk factors for recurrence of febrile seizures

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<th>Major risk factors</th>
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<td>• Age below 1 year</td>
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<td>• Duration of fever less than 24 hours.</td>
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<td>• Fever - 38°C to 39°C</td>
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<table>
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<th>Minor risk factors</th>
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<tr>
<td>• Family history of febrile seizures</td>
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<tr>
<td>• Family history of epilepsy</td>
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<tr>
<td>• Complex febrile seizures</td>
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<tr>
<td>• Day care</td>
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<tr>
<td>• Male gender</td>
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<tr>
<td>• Lower serum sodium</td>
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<tr>
<td>• Influenza A viral infection</td>
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Risk factors for recurrence of febrile seizures have been grouped into major and minor risk factors.\(^{(10)}\)

Major risk factors – age < 1 year, duration of fever < 24 hrs, fever 38-39°C.

Minor risk factors – family history of febrile seizures, family history of epilepsy, complex febrile seizure, day care, male gender, lower serum sodium, Influenza A viral infection.

### Risk factors for developing Epilepsy

Following a first FS, 2–4% of children will experience at least one unprovoked seizure, a risk four times that in the general population, and most of these children will subsequently develop epilepsy.\(^{(109-105)}\) Factors that consistently increase the risk

### Table 4: Risk factors for developing epilepsy after febrile seizures

| • Family history of epilepsy |
| • Focal complex febrile seizures |
| • Fever < 1 hour before febrile seizure |
| • Recurrent febrile seizures |
| • Presence of pre-existing neurodevelopmental abnormalities |
for developing unprovoked seizures (epilepsy) following FS, include a family history of epilepsy (18 %), focal complex febrile seizure (29 %), fever < 1 hour before febrile seizure (11 %), recurrent febrile seizures (4 %) and the presence of pre-existing neurodevelopmental abnormalities (33 %).102,106

**Prognosis**

The prognosis for children with febrile seizures is favorable. There are no long term adverse effects of having ≥ 1 simple febrile seizures. While early reports had suggested that febrile seizures were associated with sudden death, the results from a large population-based study indicate that the small excess in mortality among children with febrile seizures is restricted to those with complex febrile seizures. Simple febrile seizures do not have an increased risk of mortality.107-109 Complex febrile seizures have an approximately 2-fold long term increase in mortality, as compared to the general population over the subsequent 2 years, probably secondary to the coexisting pathology. Furthermore, the increased risk in those patients is explained, at least in part, by pre-existing neurologic abnormalities and subsequent epilepsy.110 In addition there does not appear to be any association between FS and sudden infant death syndrome. Neurologic sequelae, including new neurologic deficits, intellectual impairment, and behavioral disorder, are rare following febrile convulsions. Most population based studies have shown no obvious association between simple or complex FS, including febrile status, and the later development of neurological deficits (for example, hemiplegia), overall cognitive functioning, or specific memory impairment.111,112

**Conclusions**

Febrile seizures in children are benign events that do not have any long term neurological sequelae, and neither long term daily phenobarbitone nor intermittent diazepam have any role in the management of these children with simple febrile seizures. Appropriate education and emotional support should be provided to parents. In situations where severe parental anxiety is associated with febrile seizures, intermittent therapy may be advised; continuous antiepileptic therapy is rarely used. Recent epidemiologic studies have also confirmed that the vast majority of children with febrile seizures have a benign prognosis and a normal long term outcome.
References

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Dear Doctor,

Seizures, in a small child having fever, is a common presentation in clinical practice. When faced with a child having febrile seizures, a number of questions crop up like does the child need hospitalization, are diagnostic procedures like LP, EEG, CT Scans etc. necessary, what is the risk of the child developing epilepsy later on in life, what is the role of anti-epileptic medications in febrile seizures. Dr. Anand Shandilya and Dr. Surpreet Nagi have used their years of experience to answer these questions in a very lucid manner. We are sure, the practical tips provided by them would be very useful in your day to day practice.

This booklet is presented to you by Raptakos, Brett & Co. Ltd.

We would very much like to have your valuable suggestions and comments to make our future issues more meaningful to you.

We will appreciate if you could spend a few minutes to fill in your comments and mail the same to us. You can also view the QMR on our website : www.raptakos.com and e-mail your feedback to following e-mail id: medical1@raptakos.com

Thanking you,

Medical Director

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**Feedback form: April - June 2013 (Fever Associated Seizures)**

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2. Please suggest medical topics for our QMR which could be printed in future.

3. Any other suggestions / comments:

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   Clinical Address : ___________________________

   City : ______________ State : _____________ Pin ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

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