

## **Febrile Seizures: Four Steps Algorithmic Clinical Approach**

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Received: Sep 20, 2008; Final Revision: Jan 20, 2010; Accepted: Jan 30, 2010

### **Abstract**

Febrile seizures (FS) are the most common form of convulsive phenomena in human being and affect 2% to 14% of children. It is the most common type of seizures that every pediatrician is dealing with. It is the most benign type of all seizures occurring in childhood. There are many debates on how to approach to febrile seizures in pediatric neurology and there are many possible malpractices in this field. Some of the most common frequent queries are

- How could we differentiate FS from seizures and fever associated with serious infections involving the central nervous system?
- When should we refer the affected child for further investigations such as lumbar puncture, EEG, neuroimaging, and routine biochemical studies?
- How should we treat FS in its acute phase?
- How could we assess the risk for further recurrences as well as other risks threatening the child's health in future?
- How could we select the patients for treatment or prophylaxis?
- Which medication(s) should be selected for treatment or prophylaxis?

Trying to answer the above-mentioned questions, this review article will present a four steps algorithmic clinical approach model to a child with febrile seizures based on the current medical literature.

*Iranian Journal of Pediatrics, Volume 20 (Number 1), March 2010, Pages: 5-15*

**Key Words:** Febrile seizures; Febrile convulsions; Clinical Protocol; Algorithms

### **Introduction**

Febrile seizure (FS) is a convulsive event, exclusively occurring in childhood. The International League Against Epilepsy (ILAE) defined FS as "a seizure in association with a febrile illness in the absence of a central nervous system (CNS) infection or acute electrolyte

imbalance in children older than 1 month of age without prior afebrile seizures"<sup>[1]</sup>. The peak incidence is between 18 to 22 months of age. It is the most common form of seizures occurring in human being. It affects 2-4% (US and Europe) to 14% (Guam islands) of general pediatric population<sup>[2-8]</sup>. In which degree of body temperature does a febrile seizure occur? There

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is no cut-off point regarding this question. In fact, sometimes seizures occur before the fever. But, generally speaking when the body temperature rises over 38 °C rectally, it is considered as fever<sup>[9]</sup>. Febrile seizures are simple when they are not complex (i.e. multiple, occurring more than once during the febrile illness, prolonged, lasting more than 15 minutes, and focal)<sup>[8]</sup>. The child's prior neurologic state is not considered as a criterion for classification<sup>[1,11]</sup>.

Some interesting and yet up to date clinical findings are described by Hippocrates (460-370 BC) when he wrote:<sup>[12]</sup>

- "Children are likely to have convulsions if the fever is high".
- "These may be generalized or partial".
- "This most commonly happens under the age of seven; as they grow up they are no longer likely to be attacked by convulsions in the course of a fever". (It is interesting point because we do see children with FS older than 5 years in our practice.)
- "Particularly likely to occur during the eruption of canines" (perhaps a reference to pain-induced attacks).
- "Age of greatest vulnerability between 16 and 20 months". (On that time there was no registry or epidemiologic data rather than writer's personal experience!)
- "A positive family history is important".
- "The brain is the seat of this disease" (insight lost until the late 19<sup>th</sup> century).
- "Those suffering from brain fever (meningitis) have convulsions and some of these die rapidly".
- "Many come through safely but with minor damage" (how interesting).
- "Particularly occurs with the warm southerly winds" (a possible reference to malaria in Greece at the time).

Some authors emphasize on the temporal semiology of the febrile seizures and suggest that seizure semiology in febrile seizures deserves closer scrutiny<sup>[12]</sup>.

### How to differentiate FS from CNS infections?

This is one of the major concerns of pediatricians who are confronting a child with febrile seizures. Incidence of meningitis in children with FS is

### Key Points

Febrile seizures (FS) are the most common form of childhood seizures.

Every pediatrician usually visits these children at routine intervals.

There are two major type of FS (i.e. simple and complex)

Complex FS is a type of seizure which has one or any combination of the focality, multiplicity, and prolongation.

about 2% to 5%<sup>[6]</sup>. Lumbar puncture (LP) is an easy and convenient way to detect CNS infection; however it is an invasive method with some serious complications<sup>[13,14]</sup>. American Academy of Pediatrics (AAP) suggests LP for infants of less than 12 months and strongly recommends for infants between 12 to 18 months of age, because of the vague symptomatology of meningoencephalitis in this age group<sup>[6,14,15,16]</sup>.

Bacterial meningitis presenting as seizure with fever is more commonly seen in children with; a visit for medical care within the previous 48 hours, seizures on arrival to the emergency room, focal seizure, first complex febrile seizure, febrile status, or suspicious findings on physical or neurological examination (eg neck stiffness, petechiae or purpura, prolonged lethargy after the seizure, Kernig and Brudzinsky signs)<sup>[17,18]</sup>.

So it's quite rational to consider LP for these children. Although, these are practical guidelines for doing LP in a child with FS, we should seek for better indicators of CNS infection, especially in younger children and infants with FS.

### Indications for LP in Children with FS

A visit for medical care within previous 48 hours

Seizures on arrival to the emergency room

Focal seizure

Febrile status

Suspicious findings on physical and neurologic examination

First complex febrile seizure

Prolonged lethargy, or any altered level of consciousness after the seizure

LP: Lumbar puncture/ FS: Febrile Seizure

According to the recommendations of AAP, we should perform LP in a population in which there is only a 3-5% chance of pleocytosis (meningitis)<sup>[19,20]</sup>.

#### What other investigations are needed?

No routine laboratory examination [i.e. complete blood count (CBC), blood glucose or electrolytes including serum calcium level] is needed in a child with simple febrile seizure (SFS)<sup>[6,21-24]</sup>. If the child has additional signs or symptoms such as vomiting or diarrhea, the relevant exams will be requested. Skull X-ray, brain CT scan, and MRI are not indicated in the simple febrile seizure<sup>[6]</sup>.

There is some recent information of transient temporal lobe changes such as transient hippocampal edema in brain magnetic resonance imaging (MRI)<sup>[12]</sup>.

But these changes do not have any predictive value. It is also unclear that brain MRI is indicated in the prolonged and/or focal seizures<sup>[25,26,27]</sup>. Electroencephalography (EEG) has a limited value in the work-up of FS. Even if it is abnormal, it is not highly predictive and in fact in the children with complex febrile seizures, EEG may be abnormal in many cases<sup>[28,29]</sup>. Even newer neurophysiologic techniques such as magnetoencephalography (MEG) reveals a substantial variety of abnormalities in children with febrile seizures, but like EEG it has a limited predictive value for further recurrences or even epilepsy<sup>[30]</sup>. Some trace elements (e.g. zinc) maybe decreased in the serum of children with febrile seizures, but there is not enough evidence in the literature to apply this finding to diagnostic as well as therapeutic guidelines in children with FS<sup>[31]</sup>.

#### Investigations which are not routinely indicated in SFS

Routine blood count or biochemical lab exams  
Skull X-rays, brain CT scan and MRI  
EEG or MEG

SFS: simple febrile seizure/ MRI: magnetic resonance imaging/ EEG: Electroencephalography/  
MEG: magnetoencephalography

#### How should we treat FS in its acute phase?

Febrile seizures are usually benign and self-limiting attacks (often lasting less than 10 minutes) and protective measures are merely required. Appropriate posturing (lateral recumbent, with head extension), and keeping airways open are the recommended maneuvers for the affected children. Rectal diazepam is a good and reliable way to control seizures outside of the hospital and even at home<sup>[32,33,34]</sup>, but it should be used with great caution and in the hands of well-trained caregivers and/or parents. Parents of children with the history of prolonged and/or multiple FS, and those who are living far from medical care, should be educated and trained to use rectal diazepam. For many parents, the availability of rectal diazepam will relieve their anxiety even though they may never use that<sup>[35,36,37]</sup>.

When a child comes to emergency room with seizure, an IV route should be obtained and intravenous diazepam should be administered.

When intravenous access is difficult, rectal diazepam would be an effective alternative choice<sup>[32,34]</sup>. If the seizures continue after a sufficient dose of intravenous diazepam, a full status epilepticus treatment protocol should be initiated<sup>[38,39]</sup>.

#### Treatment of febrile seizures in its acute phase

Airways open and appropriate positioning  
Rectal and/or intravenous diazepam  
If seizures continue, try full status epilepticus treatment protocol

#### Four steps' model of approach to the children with history of febrile seizure

For practical purposes, I have proposed a four steps clinical approach to children with febrile seizures. These steps are; data gathering (i.e. formulating a database), risk assessment, patient selection, selection of treatment strategy.

##### Step 1: Formulating a database

In this step, physician gathers the clinical as well as the paraclinical relevant information to formulate a robust database.

#### 4 Steps Approach in Febrile Seizure

- Step 1: Formulating a database
- Step 2: Risk assessment
- Step 3: Patient selection
- Step 4: Selection of the treatment strategy

Following information are mandatory:

- Age of the patient
- History of febrile seizure in the 1<sup>st</sup> as well as 2<sup>nd</sup> degree family
- History of any developmental delay History of nursery admission for more than 30 days
- Day care attendance
- Duration between the beginning of fever and the occurrence of seizure
- Complexity (i.e. focal, multiple, and prolonged FS)
- Duration of postictal phase
- Presence of any neurologic or developmental deficits
- Presence of papilledema
- Nonspecific and vague symptomatology in infants less than 18 months old (eg agitation, bulging fontanel, excessive cry)
- Neck stiffness, Kernig and/or Brudzinsky signs
- Petechiae and/or purpura

#### Step 2: Risk Assessment

Risk assessment is according to the patient's database. What are the risk factors for the first FS, recurrence(s), and epilepsy in children with FS? And how important are these risk factors in our decision-making?

**Risk factors in the first febrile seizure:** In two independent studies<sup>[40,41]</sup>, the risk factors associated with the 1<sup>st</sup> FS are; history of FS in the 1<sup>st</sup> or 2<sup>nd</sup> degree family members, nursery stay of more than 30 days, developmental delay, attendance at day-care, high peak temperature. In the second study, there was an inverse association between gastroenteritis, as an underlying disorder, and first attack of febrile seizure. There was a 28% chance of at least one febrile seizure for children with two or more of the above mentioned risk factors<sup>[40]</sup>.

**Risk factors in recurrences of febrile seizures:** The chance of recurrence of febrile seizures is about one in three regardless of any

risk factors<sup>[42-45]</sup>. The most common consistent risk factors are a family history of FS and age of onset of less than 18 months<sup>[42-45]</sup>. Two other definite risk factors are peak temperature<sup>[43,44,46]</sup> and duration of the fever before the seizure<sup>[2,47]</sup>.

The higher the peak temperature, the higher chance for recurrence. It is very important to mention that the peak temperature is not the temperature at the time of seizure or arrival at the emergency department, but it is the peak temperature during the whole febrile illness period. The other related risk factor is the duration of febrile illness before the seizure. The shorter the duration, the higher is the risk of recurrence of further seizures. Children with multiple risk factors have the highest chance for recurrence<sup>[43,47]</sup>. A child with two or more risk factors has a greater than 30% chance for recurrence at two years; a child with three or more risk factors has a greater than 60% chance for recurrence<sup>[47]</sup>. In children with no risk factor, there is a recurrence risk of less than 15% at two years. A recurrent febrile seizure also tends to be prolonged if the first attack was prolonged<sup>[10,44]</sup>.

Presence of family history of afebrile seizures (epilepsy) is a doubtful risk factor for recurrence of further febrile seizures<sup>[43,44,48,49]</sup>, so I am not going to discuss on or consider it here.

Neurodevelopmental delay, complex FS, sex, and ethnicity are not considered as a risk factor for recurrence of FS<sup>[4,10,43,44,48,49]</sup>.

**Risk factors for subsequent epilepsy:** About 2%-10% of patients with FS will later develop epilepsy<sup>[2,4,5,50,51]</sup>. The occurrence of family history of non-febrile seizures as well as the occurrence of complex FS will raise the risk of subsequent epilepsy<sup>[2,4,5,50,51]</sup>. In two studies, there was a slightly increased risk in children with multiple FS<sup>[2,51]</sup>. One study found an inverse association between the duration of fever before the seizure and occurrence of further epilepsy<sup>[51]</sup>. That means the shorter the duration between the onset of fever and seizure, the higher the chance of developing further epilepsy. Two studies revealed that the children with very prolonged febrile seizures (ie febrile status) are more prone to develop further epilepsy<sup>[2,51]</sup>. The only common risk factor for both recurrence of FS and epilepsy is the duration of fever before the onset of febrile seizure<sup>[48,49,51]</sup>.

**2<sup>nd</sup> Step; Risk Assessment for FS Recurrences**

- **Definite Risk Factors**

- Family history of FS
- Age <18 months
- Low peak temperature
- Duration of fever

- **Possible Risk Factor**

- Family history of epilepsy

- **Not a Risk Factor**

- Neurodevelopmental abnormality
- Complex FS
- >1 complex feature
- Sex
- Ethnicity

*No risk factor; <15% chance of recurrence at two years  
2 or more risk factors; >30% chance of recurrence at two years*

*3 or more risk factors; >60% chance of recurrence at two years*

Febrile seizure could be the initial presentation of some malignant childhood epileptic syndromes such as Dravet syndrome or severe myoclonic epilepsy of infancy<sup>[52]</sup>.

**Mortality and morbidity:** No mortality has been reported with FS according to several studies<sup>[3,4,53,54,55]</sup>. Even in a very prolonged FS (febrile status), there is little chance for death<sup>[38,56-61]</sup>. There is also no report indicating morbidity such as motor deficit and/or cognitive impairment<sup>[3,4,53-60]</sup>. Even prolonged febrile seizures are not associated with cognitive deficits<sup>[55,59,62]</sup>.

### **Step 3: Patient Selection (who should be treated?)**

The 3<sup>rd</sup> step is patient selection for prophylaxis or treatment. In other words, who should be treated after the risk assessment? As previously mentioned, there is no reported mortality or morbidity after FS. The risk of further occurrence of non-febrile seizures is considerable but there is no way to prevent epilepsy in a child with FS<sup>[48,63-66]</sup>. The relationship between FS and temporal lobe sclerosis is yet controversial<sup>[25,67]</sup>. Only there are some concerns about prolonged or atypical febrile seizures especially those with a pre-

**Who should be treated?**

When the patient is pretty far from medical facilities.

When the patient has preexisting neurological deficit with prominent temporal semiology.

When the patient has three or more risk factors for recurrence of FS (a 60% chance for further recurrences).

existing temporal or hippocampal pathology<sup>[12,68-74]</sup>. Maybe the only strong rational for prophylaxis in children with FS, is preventing the parental awful experience of "feeling dead" when they witness their own child's convulsion<sup>[75]</sup>.

So we prefer to prevent further recurrences of FS in the following cases:

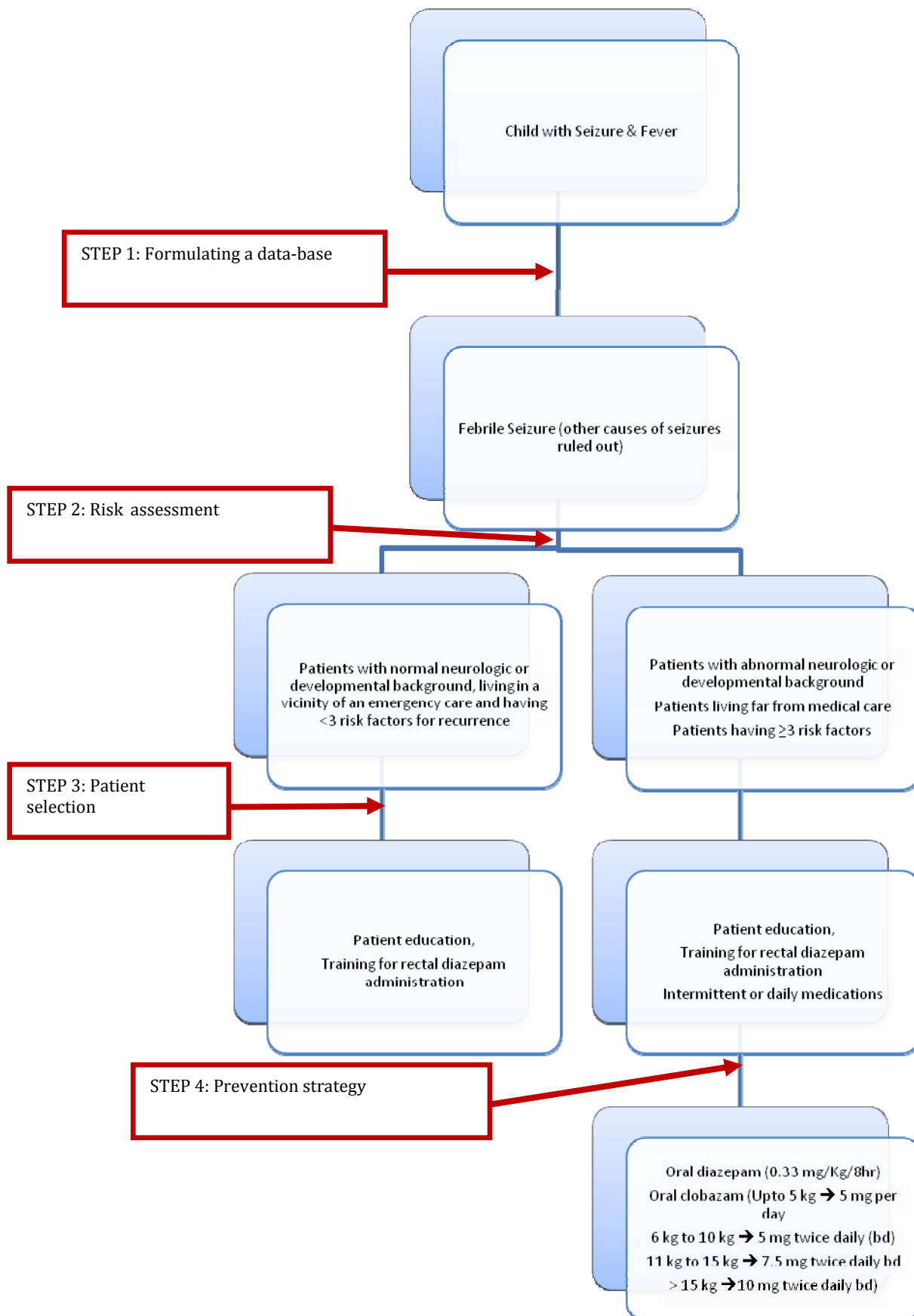
- When the patient is pretty far from medical facilities.
- When the patient has preexisting neurological deficit with prominent temporal semiology.
- When the patient has three or more risk factors for recurrence of FS (a 60% chance for further recurrences).

### **Step 4: Drug Selection (Treatment Policy)**

The best treatment policy is patient (parental) education about the benign nature of FS and the risks and benefits of any medication<sup>[76]</sup>. Parents' education, regarding how to deal with the convulsing child as well as some simple and clear explanations about febrile seizures and their benign nature and outcome are all that is necessary<sup>[75]</sup>. Teaching parents how to use rectal diazepam in an emergency condition at home is quite beneficial<sup>[32]</sup>. So they can administer it whenever their child seizes. Maybe this is the most reliable and convenient type of treatment. There are some evidences that intranasal or intrabuccal administration of midazolam is also effective in cessation of febrile seizures<sup>[77,78]</sup>.

For long-term treatment, there are mainly two types; intermittent medication at the time of fever, and daily (continuous) medications.

There is not enough evidence that antipyretics would reduce the risk of seizures in a febrile illness<sup>[79,80]</sup>. But it is quite rational to use antipyretics in a febrile illness episode because



**Fig. 1:** Four steps' model of approach to the children with history of febrile seizure



of parental feelings of anxiety and guilt. There are strong evidences that intermittent use of oral or rectal diazepam is effective in preventing the seizures in a febrile episode<sup>[42,81-85]</sup>. It is recommended to use oral diazepam in a dose of 0.33 mg/kg/dose every 8 hours from the onset of a febrile illness. But potential side effects of diazepam in such a high dose (ie sedation and ataxia) should be considered. There are some studies indicating that intermittent clobazam could be as effective as diazepam in preventing the seizures in a febrile illness, but ataxia is less prominent than with diazepam<sup>[86,87,88]</sup>.

Intermittent administration of phenobarbital is ineffective in preventing the febrile seizures<sup>[89,90]</sup>. Phenobarbital has been used as a daily basis for prevention of further recurrences of FS. Its effectiveness has been proved by some studies in this regard<sup>[80,83,84,91-94]</sup>. In therapeutic doses, phenobarbital may induce hyperactivity and behavioral disorders<sup>[95,96]</sup>. Even in some studies its effectiveness in preventing the further febrile seizures is doubtful<sup>[95,96,97]</sup>. So the use of Phenobarbital is not recommended as a means for prevention of further febrile seizures.

Sodium valproate is also effective in preventing further febrile seizures<sup>[84,93,94,98]</sup>. However, its use is not indicated because the children who are at highest risk for recurrences are also most vulnerable to idiosyncratic hepatic toxicity as the drug's side-effect<sup>[99,100]</sup>.

There are some reports indicating that topiramate could protect the blood brain barrier in the experimental model of febrile seizures and may have some protective effect in children with febrile seizures<sup>[101,102,103]</sup>. But there is not enough evidence to use this drug in the practice. There is also no report on newer anticonvulsive agents and their effectiveness as prophylactic measures in febrile seizures.

### Conclusions and algorithmic four steps approach to children with FS

Febrile seizures are the most common as well as most benign type of seizures seen in infants and children. Every pediatrician should be familiar with it and adopt a uniform and regular approach to this common phenomenon.

According to the current medical literature the most important role of physicians in this

regard is acting as a knowledgeable, trustworthy, sympathetic educator. They should help the parents to know more about the condition and act properly in a convulsive state.

Rectal diazepam is a good treatment modality in acute phase of seizure and parents should be trained to administer it in an emergency condition. Prophylaxis of further attacks by other drugs is not justified in every case. Based on current medical literature, an algorithmic model is proposed, introducing a four steps approach.

**Conflict of interest:** None

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## CME QUESTIONS

**1- What are the main types of febrile seizures?**

- I. Simple and atypical
- II. Simple and complex
- III. Complex and atypical
- IV. Simple and non-typical

**2- According to the paper which one of the followings is an indication for lumbar puncture in a child with seizure and fever?**

- I. Focal seizures
- II. 2<sup>nd</sup> complex febrile seizure
- III. Lethargy after the seizure
- IV. Post-ictal sleep

**3- You are visiting a 22 months old boy with seizure and fever. He has had diarrhea and fever from yesterday. The seizure was a generalized tonic clonic one lasting for about 5 minutes, without any post-ictal signs. Neurologically he is quietly normal. Which one of the following investigations is indicated?**

- I. EEG
- II. Skull x ray
- III. Brain MRI
- IV. Serum electrolytes

**4- A child who had a simple febrile seizure with a positive family history of febrile seizure (the father). He is 2 years old and the peak temperature was 40 °C. Please assess the risk for further recurrences for febrile seizure(s)?**

- I. 15%
- II. 30%
- III. 45%
- IV. 60%

**5- Who should be treated for further recurrences of febrile seizures?**

- I. One who had more than one febrile seizure.
- II. One who had multiple FSs in a day.
- III. One who lives far from medical care.
- IV. One who is developmentally normal.

**You can find correct answer in page**