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Management of simple febrile seizures

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Introduction

Febrile seizures (FS) are by far the commonest form of childhood seizures between the ages of 6 and 60 months[1]. They occur in the setting of a febrile illness but in the absence of evidence of an intracranial infection or associated metabolic disturbance, in a child with no history of preceding afebrile seizures[2]. Although 6 months to 6 years is considered the general age limit, even a younger age limit is acceptable in the setting of no likely explanation for the seizure other than a FS[3]. According to the International League against Epilepsy definition, the lower age limit is considered to be as young as one month[3]. FS affect 2-5% of children in the at risk age group. This figure is reported to be higher in some Asian countries (8% in Japan and 16% in China)[4]. They usually do not have any adverse effect on motor development or long term cognitive outcome[5].

FS are subdivided into 2 categories: simple and complex. Simple FS are common accounting for more than 70%[6]. They last for less than 15 minutes, are generalized (without a focal component), and occur once in a single febrile illness. Complex FS account for the balance 30%, are prolonged (>15 minutes), and/or focal, and/or occur more than once in a single febrile illness[2]. Complex FS sometimes may also have evidence of post seizure neuronal dysfunction such as Todd paresis which may last minutes to hours to even a few days[7]. Within the complex FS group, those which are prolonged and evolve into status (febrile status epilepticus) account for 5% of all FS[6]. This article is focused on the management of simple FS, especially on the aspects related to primary care at the time of presentation.

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The main expected outcomes of this article are:

1. Improving paediatrician's understanding of the scientific basis for using or avoiding various proposed treatments for children with simple FS.
2. Avoiding some forms of therapy with high potential for adverse effects and no demonstrated ability to improve children's long-term outcome.
3. Helping the practitioner educate caregivers about the low risks associated with simple FS.

These are very similar to the objectives outlined by the American Academy of Paediatrics in their last guideline on long term management of simple FS[8]. This article intends to achieve these outcomes through discussion on the following aspects which are often mismanaged during acute presentations of FS and during subsequent febrile illnesses.

1. Recommended neurodiagnostics when a child presents with a simple FS.
2. Role of regular antipyretics in those with a risk of recurrence of FS.
3. Role of intermittent anticonvulsant therapy during future febrile illnesses for prevention of recurrences.
4. Role of long term anticonvulsant prophylaxis in those with recurrent FS.
5. Management of the acute FS.

Based on the quality of evidence as indicated by levels A-D and X, the levels of recommendation are divided into *strong recommendation*, *recommendation, option* and *no recommendation* as shown in figure 1. This will help the reader to appreciate the strength of the different recommendations made in this document and the quality of evidence that is available to support such recommendations. These levels were adapted from the recent guideline on long term management of simple FS from the American Academy of Paediatrics[8] and the guideline on neurodiagnostics[9].

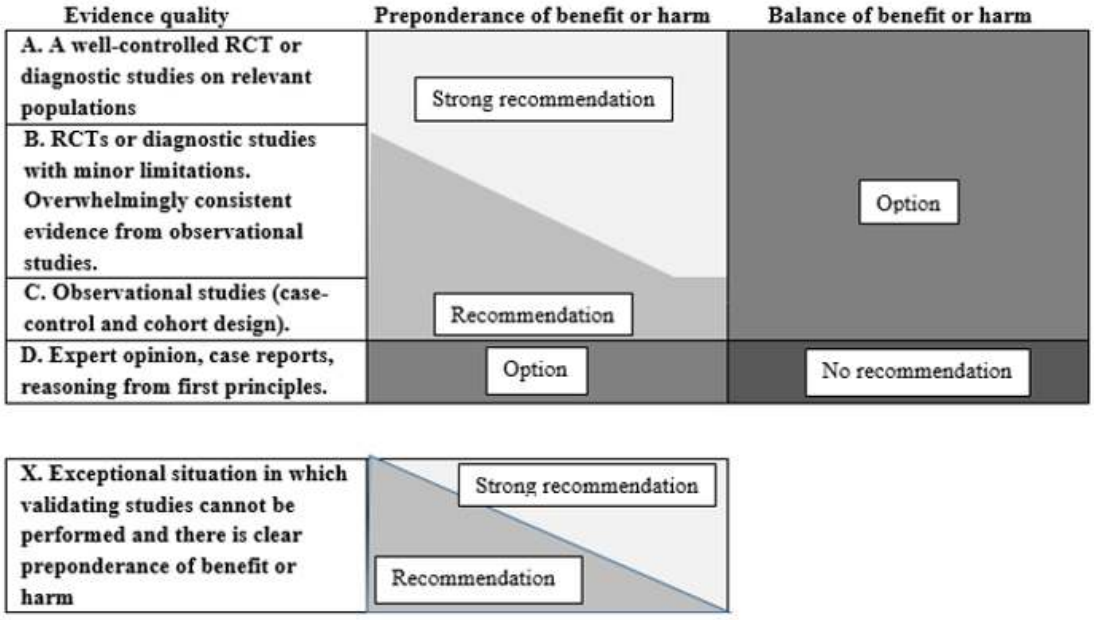

Figure 1: ***Integrating evidence quality appraisal with an assessment of anticipated balance between the benefits and harm if a policy carried out leads to designation of a policy as a strong recommendation, recommendation, option or no recommendation***

Recommended neurodiagnostics in a child presenting with simple FS[9,10,11]

When a child presents with a simple FS, some investigations are done unnecessarily and even repeatedly, while some other useful investigations for evaluation of the differential diagnosis are seldom done[12]. These neurodiagnostics are discussed under 4 different groups of investigations:

1. When to do a lumbar puncture.
2. Role of electroencephalography (EEG) in confirming or identifying the cause for FS.
3. Doing blood investigations for identification of the cause for FS.
4. Role of neuro-imaging in the routine evaluation of a child with simple FS.

When to do lumbar puncture (LP)

- ***It should be done*** in any child who presents with a seizure ***and*** has any symptoms or signs suggestive of meningitis or central nervous system (CNS) infection. ***Level B evidence: Strong recommendation, overwhelming observational studies.***
- **It is *an option*** when an infant between the ages of 6 and 12 months presenting with a seizure and fever when the child is considered deficient in immunity against *Haemophilus influenzae* type B infection or *Streptococcus pneumoniae* infections or when the immunization status cannot be determined because of an increased risk of meningitis. ***Level D evidence: Optional; Expert opinion and case reports***
- An LP is ***an option*** in the child who presents with seizure and fever after being pre-treated with antibiotics which can mask the signs and symptoms of meningitis. ***Level D evidence: Optional***
- It is important to maintain a lower threshold for doing an LP in the younger age group since clinical features of meningitis may not be robust in this age group.

Role of EEG in the routine evaluation of child with simple FS

- EEG should ***not be done*** in a neurologically normal healthy child presenting with FS. ***Level B evidence: Strong recommendation, overwhelming observational studies***
- History of prematurity or developmental delay per se should not be an indications to do an EEG when a child in the designated age group presents with an otherwise unremarkable simple FS. Doing an EEG in an infant or toddler is difficult, time consuming and requires sedation in most instances. The interpretation of sleep EEGs unless by a neurophysiologist or paediatric neurologist, may result in increased false positive findings.
- There is no evidence that EEG readings done either at the time of presentation after a simple FS or within the following month are helpful in predicting a risk of either recurrence of FS in the future or risk of the

development of epilepsy within the next 2 years[13]. Further, there is no evidence to indicate that any interventions made based on the findings in the EEG would alter the child's outcome in relation to development of epilepsy later in life[14].

Routine blood investigations in a child presenting with FS

- In children presenting with FS, it is ***not recommended*** to carry out investigations which are done ***routinely*** to investigate the underlying cause when children present with afebrile seizures. These blood investigations include serum calcium, phosphorus and magnesium levels, serum electrolytes, random blood sugar level and complete blood count. ***Level B evidence: Strong recommendation, overwhelming observational studies***
- Investigating the cause of the underlying infection can be done if deemed necessary. Complete blood cell count may help to identify those at risk of bacteraemia. However, incidence of bacteraemia in children less than 24 months is the same whether they present with or without seizures[15]. Thus the clinician may use it and other laboratory tests such as urine full report at his/her discretion to establish the cause of the fever. Capillary blood sugar assay is indicated if the child appears sick.

Role of neuroimaging

- Routine neuroimaging should ***not be done*** in children who present with FS. ***Level B evidence: Strong recommendation, overwhelming observational studies.***

- Although parents may sometimes want neuroimaging carried out to explain the reason for the seizure, they should be reassured that neuroimaging is most often normal even in epileptic children. They should be informed that these tests carry risks such as radiation in the case of computerized tomography, are difficult to carry out in children without sedation and that these imaging findings will not alter the outcome of their child. Clear explanation about the pathogenesis of febrile seizures, may help them understand why these investigations are not useful.

Role of using antipyretics during febrile illness to prevent occurrence of FS

The pathogenesis of FS indicates an age dependent increased firing of cortical circuitries as a response to the excitatory neuro-transmitters secreted in response to the underlying infection[16]. Fever is rather another clinical sign related to the underlying illness but not the cause of the seizure and therefore overzealous control of temperature is unlikely to prevent recurrence of FS[17]. There are several clinical trials that have investigated the role of regular antipyretics as a measure to prevent recurrence of FS. None of them have shown that administering regular acetaminophen and even ibuprofen[18], prevents recurrence of FS[17]. Therefore, administration of regular antipyretics including ibuprofen is ***not recommended*** in a child with a history of FS during subsequent febrile illnesses. ***Level B evidence: Strong recommendation, overwhelming observational studies***

This recommendation applies to other measures to reduce the temperature as well. One example is tepid sponging, which is not thought to be beneficial in preventing recurrence of FS though this is not proven with a clinical trial. Use of these measures may help to make the child feel comfortable only but not prevent recurrence of a seizure[14]. Conveying accurate information to the parents on the role of antipyretics will help to reduce unwarranted fear of fever in them[19].

In the Sri Lankan setting, various unproven and non-recommended strategies are used to reduce the temperature. Prescription of non-conventional antipyretics including nonsteroidal anti-inflammatory drugs (NSAIDs) is noticed. Similarly, in the hospital and/or at first contact settings, the need for continued tepid sponging to reduce temperature is emphasized. Both these practices ***should not be recommended***. The practice of frequent tepid sponging often results in great discomfort to the sick child. It may also result in increasing the core-periphery temperature gap which may then result in generation of chills to increase body temperature. Sometimes this may be mistaken for persistence or seizure activity.

Role of intermittent anticonvulsant therapy during future febrile illnesses for prevention of recurrences

The general risk of recurrence following one simple FS varies between 30-40%[2]. Identified risk factors for recurrence are: a). Early age of onset (<15 months) b). FS in first degree relatives c). Frequent febrile illnesses in those attending day care d). Low temperature at the time of the first FS and e) first complex febrile seizure[20,21].

The recurrence frequency is 10% in patients with no risk factors but increases to 25–50% in the presence of 1–2 risk factors[21]. It may increase further to 50–100% in the presence of 3 or more risk factors[21]. Avoiding frequent febrile illnesses is the only modifiable risk factor.

The recurrence of FS does not alter the prognosis of a child who had been neurologically normal before the onset of the first FS. Therefore, the need of any prophylactic therapy needs detailed discussion with parents. In those deemed desirable, intermittent use of anticonvulsants during early stages of a febrile illness is described to reduce the risk of recurrence of FS. Oral or rectal diazepam and oral clobazam are those that have been trialled as intermittent therapies[22]. It is best recommended to be used on a selective policy in those with increased risk of recurrence[21]. Some studies have shown reduced recurrences with diazepam but in others the findings were controversial[22]. It is not beneficial in those with low risk for recurrence[21]. A meta-analysis which reviewed 45 papers describing prophylaxis for FS concluded that overall, use of oral diazepam was ineffective in preventing recurrences[23]. Looking at the "number needed to treat to prevent one recurrence" they concluded that it requires treatment of 26 children with diazepam to prevent one recurrence. Comparison of the two benzodiazepines diazepam and clobazam, shows no difference in efficacy but advantage of less sedation in clobazam in comparison to diazepam[24].

Even if some studies describe benzodiazepines as being effective for reducing recurrences, side effects related to them are unavoidable. These include drowsiness, transient mild ataxia, hyperactive behaviour, lethargy, irritability etc.[21]. The doses and the duration of diazepam in these studies varied from 0.2 mg/kg/day to 1 mg/kg/day and 48 hours to entire duration of the febrile illness respectively[22]. Considering the above factors of side effects and the number needed to treat to prevent a recurrence in the context of a rather benign condition (where there will be no permanent damage and eventual spontaneous remission) ***prophylaxis for simple FS recurrence is not recommended (Class of evidence I)***[9]. Further, it is also considered to be not cost effective for both patient and hospital when taking into account the need for hospitalization and investigations when the febrile child becomes less active and drowsy with the benzodiazepines. In a randomized clinical trial using diazepam and clobazam, the mean durations of hospital stay during illnesses in the treated children were 6.0±1.0 and 4.6±0.08 respectively[25].

Considering all the above reasons, all guidelines on management of simple FS as well as the latest Cochrane review ***do not recommend*** use of intermittent prophylaxis routinely[8,22,23,26,27]. ***Level B Evidence. Strong recommendation, overwhelming observational studies.***

Role of long term anticonvulsant prophylaxis in those with recurrent FS

Simple FS have a benign course and the affected children eventually outgrow these seizures when age advances. These seizures have not been shown to affect the child's long term neurological or intellectual capacity[5]. The use of long term prophylaxis will not alter the future risk of development of epilepsy either, since these medications do not play a role in control of long term epileptogenesis. On the other hand, use of medication on a daily basis in a small child is inconveniencing both parent and child. Another question related to the use of these anti-epileptic drugs is how long to give them, since FS can recur up to the age of 5-6 years.

The anticonvulsants that have been used often for long term prophylaxis are sodium valproate and phenobarbitone[22]. Although they are effective in preventing recurrences, regular use of long term therapy for simple FS is not recommended due to the adverse effects which overcome the benefits of giving these medications[8,22]. Phenobarbitone is known to cause significant adverse effects and its use is questioned due to the effect on cognition outlasting stopping of medication by several months[28]. It also causes irritability, behavioural disturbances and sleep disturbances. Sodium valproate in the younger age should be used with caution due to the rare association with fatal hepatotoxicity. Further, this too causes effects on cognition and behaviour. Therefore there is ***no evidence*** to support treatment of simple FS with continued prophylaxis[22,27]. ***Level B evidence, Strong recommendation, overwhelming observational studies.***

Conservative management of the seizure with correct positioning, airway safety etc. only is advocated since most simple FS abort spontaneously within about 2-3 minutes[29]. In the case of seizures lasting more than five minutes, use of abortive medications such as per rectal diazepam or intranasal or buccal midazolam is recommended[29]. In our setting, midazolam is not yet available in the buccal or nasal form. However, if facilities are available for quick transport to a hospital and if the parents are competent in managing per rectal diazepam administration, this is one possible option. Unlike in the past, there are parents who are well read about FS and have access to transport in an emergency. Therefore this option should be taken up with the parents if they wish to do so. The much feared respiratory depression is rare and minimal if the appropriate dose is administered[30].

The general recommendation is against use of prophylaxis both intermittent and long term; however, there is room to consider them on an

individual basis or if the physician identifies benefit for the patient over and above the many potential disadvantages related to therapy. Few examples of such exceptional situations include: absence of a reliable caregiver to manage the child during a seizure, long distance to travel for medical attention in case of prolonged seizures, "unacceptable" high frequency of FS and extremely anxious parents.

Although not researched as an intervention, the most important reason for recurrence of FS is recurrence of infections. Some particular viral infections are known to cause a higher risk of recurrence[31]. One way of preventing FS would be to minimize infection. This can be tried by parents using regular hand washing, preventing exposure to pathogens unnecessarily by avoiding crowded places etc. It has also been described that iron deficiency, which is common in Sri Lankan children is associated with moderately increased risk of FS[32]. Detecting this from a routine blood film and iron status studies is recommended. Zinc deficiency is also considered a risk factor[33].

Management of the acute febrile seizure

This article is limited to management of children with simple FS only. In this group, duration of seizure is short and it often abates spontaneously within 2-3 minutes. Management is often limited to addressing the basic lifesaving manoeuvres. Turning the child to a side and keeping in the recovery position is important. Slight elevation of the head with tilt to the lateral side will prevent aspiration. Sucking out secretions can clear the airway.

Careful observation of the clinical semiology by the attending medical officer is important. This will facilitate identification of the seizures with focal features. ***It is not recommended to wet the child during the seizure.*** Administration of rectal antipyretics will not help control the seizure either. After waiting for ***5 minutes*** for possible spontaneous resolution, drug administration for control of seizure should be initiated. Rectal (0.5mg/kg) or intravenous (0.25 mg/kg) diazepam has been used for effective acute control of seizures[34]. Midazolam is another benzodiazepine which is available for acute control of FS. It has the advantage of being equally effective as intravenous (IV) diazepam even when administered through non intravenous routes i.e. nasal (0.2-0.5 mg/ kg), buccal (0.5 mg/ kg) and intramuscular (0.2 mg/kg)[35]. In fact, some of the more recent literature indicate faster control of seizures following intramuscular[36] midazolam than with IV diazepam[30], which may be partly due to the ease of administration. The IV preparation of midazolam is available in the national health care system but appears to be less frequently utilized. Although we do not have the nasal and buccal formulations, pharmacologists do not disapprove of the use of the IV preparation until nasal and buccal formulations are available locally. An important aspect requiring attention and emphasis is timely administration of these medications when seizures do not stop within the first 5 minutes. This will help early control of the rare (5%) but potential febrile status epilepticus which is implicated in the subsequent development of epilepsy.

Another essential component of the management of simple FS is health education of parents. In order to practise this better and more often, it is essential to cover the following points:

1. Describe the features of FS. Explain the difference between simple and complex FS.
2. Explain the age dependent nature of these seizures.
3. Help parents understand the risk factors for development of FS and what reasons contribute towards recurrence in their child.
4. Give correct advice regarding the pathogenesis of FS so that they do not unduly fear about fever in their child.
5. Measures to be taken during a future recurrence should be explained. Ability to stay calm and notice as many features as possible should be encouraged.
6. If prophylactic medications are considered, weigh the benefits over the risks of side effects.
7. Reassurance regarding the benign nature of simple FS is important.

This article aims to provide an evidence based background for management of simple FS. This may be a win-win situation to both practitioner and the parent. On the one hand, a clear understanding of available evidence will help the paediatrician to manage affected children correctly with confidence. On the other hand, educating the parent on the relative harmless outcome of the condition will alleviate their anxiety and avoid unnecessary medication of their children.

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