Febrile seizures: emergency medicine perspective

Amir A. Kimia[a], *Richard G. Bachur*[a], *Alcy Torres*[b], *and Marvin B. Harper*[c]

Purpose of review
The review describes current evidence on the evaluation of febrile seizures in the acute setting, the need for further outpatient assessment, and predictors regarding long-term outcomes of these patients.

Recent findings
New evidence has been added in support of limited assessment and intervention: evidence on low utility of lumbar puncture, emergent neuroimaging, and follow-up electroencephalography, as well as low yield for antipyretic prophylaxis and intermittent use of antiepileptic drugs. Finally, there is growing evidence regarding the genetic basis of both febrile seizures and vaccine-related seizures/febrile seizures.

Summary
Routine diagnostic testing for simple febrile seizures is being discouraged, and clear evidence-based guidelines regarding complex febrile seizures are lacking. Thus, clinical acumen remains the most important tool for identifying children with seizures who are candidates for a more elaborate diagnostic evaluation. Similarly, evidence and guidelines regarding candidates for an emergent out-of-hospital diazepam treatment are lacking.

Keywords
complex febrile seizures, febrile convulsions, febrile seizures

INTRODUCTION

Two thousand years after being described by Socrates, the definition of the syndrome referred to as febrile seizure is still evolving. Currently, febrile seizure is defined as age-specific seizures associated with a temperature of 38.0°C or higher, unprovoked by central nervous system (CNS) infection, trauma, or metabolic abnormality [1].

Definitions and terminology

The National Institutes of Health (1980) defined febrile seizure as follows: an event occurring in infancy or childhood, usually between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause [2].

The International League Against Epilepsy (1993) defined febrile seizure as a seizure occurring in childhood after age 1 month, associated with a febrile illness not caused by infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria of other acute symptomatic seizures [3].

Most recently, the American Academy of Pediatrics (AAP) (2008) defined febrile seizure as a seizure occurring in febrile children between the ages 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of a febrile seizure.

Febrile seizure is further classified into either simple or complex [4]. Simple febrile seizure is defined as generalized, lasting less than 15 min, comprising generalized tonic and clonic activities without a focal component, and without recurrence within 24 h (± within the same febrile illness). Complex, atypical, or complicated febrile seizure (CFS) [5] is defined by having the following features: partial onset or focal features, and/or duration longer than 15 min, and/or recurrence within 24 h, and/or association with postictal neurological abnormalities, such as Todd paresis.

[a]Division of Emergency Medicine, Boston Children's Hospital, [b]Pediatric Neurology, Boston Medical Center and [c]Division of Emergency Medicine, Pediatric Infectious Diseases, Boston Children's Hospital, Boston, Massachusetts, USA

Correspondence to Amir A. Kimia, MD, Division of Emergency Medicine, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA. Tel: +1 617 355 6624; e-mail: amir.kimia@childrens.harvard.edu

Curr Opin Pediatr 2015, 27:292–297
DOI:10.1097/MOP.0000000000000220

KEY POINTS

- New evidence validates the concept of minimal intervention and evaluation of febrile seizure, given low utility of routine testing and treatment.
- Clinicians should familiarize themselves with predictors of recurrence and/or unprovoked seizures to better inform and direct families.
- Future directions include further progress in genetic studies, as well as evidence to inform guidelines for CFS, febrile status epilepticus, and criteria for out-of-hospital 'rescue' benzodiazepine prescribing.

Prevalence genetics and environment

Febrile seizures occur in 2 to 5% of children who are 6 months to 5 years of age, with peak incidence at 18 months of age and low incidence before 6 months or after 3 years of age. There is no gender difference [6], yet there is a higher rate of febrile seizure in Asian populations [7]. Febrile seizures follow a bimodal seasonal pattern or simply mirror peaks of febrile respiratory infections (November–January) or gastrointestinal infections (June–August).

Two-thirds of febrile seizure cases seen in emergency departments (EDs) are simple febrile seizures. Among CFS cases, the complex features are focality (16%), multiple seizures (14%), and prolonged duration (9%). Two complex features are seen in 6.5% of individual cases and three features in less than 1%. Febrile status epilepticus (duration greater than 30 min) represents about 5% of febrile seizure.

Febrile seizure occurs more often in first-degree and second-degree relatives of children with febrile seizure [8], with about 20% among siblings and 10% among parents. The mode of inheritance is multifactorial, although an autosomal dominant mode of inheritance has been reported [9].

EMERGENCY DEPARTMENT EVALUATION

ED assessment focuses on identifying a fever source, immunization, and recent antibiotic use. In addition, the seizure features and possible risk factors must be addressed: seizure type, duration, any prolonged postictal phase, and family history of febrile seizure or epilepsy [10▪]. This information will guide the need for infectious workup, imaging, consideration of rectal diazepam prescription on discharge, and a subsequent electroencephalography (EEG). Physical examination should not be deferred until the postictal state has resolved; although limited, it may reveal a Todd's paresis that would otherwise go unnoticed. Meningeal signs and a child's level of consciousness should be assessed serially until the child is back to baseline.

Lumbar puncture

Seizure is a known presenting symptom and predictor of acute bacterial meningitis (ABM) [11], yet it is unlikely to be the sole manifestation of ABM [12]. Routine lumbar puncture among children with febrile seizure has been shown to be of limited value [13–15] for both simple and CFS [16,17▪]. Although complex features increase the risk of ABM when compared with simple febrile seizure (data from the developing world suggest rate of ABM among first-time febrile seizure to be under 1% for simple febrile seizure and nearly 5% in a CFS [18]), the overall ABM rate for CFS in the USA is too low to recommend routine lumbar puncture. However, lumbar puncture may be indicated with concerns of altered mental status beyond the transient postictal state, critically ill children including those who are intubated and sedated, and when there are features raising the possibility of CNS infection.

The 2011 AAP guidelines suggest lumbar puncture in children with simple febrile seizure with signs and symptoms of ABM (e.g., neck stiffness, positive Kernig's and Brudzinski's signs), in those younger than a year of age if they did not receive their routine immunizations or the immunization status is unknown, and in those who were pretreated with antibiotics, as a result of the potential masking of some signs and symptoms of meningitis. ABM rates described in the developing world may justify guidelines different than those applied in the USA.

Other laboratory testing

The 2011 AAP recommendations do not routinely recommend serum electrolytes, blood glucose, or complete blood count because of low yield [19–21,22▪]. Iron deficiency is known to be associated with febrile seizure [23], yet this standalone factor should not necessarily prompt a complete blood count in the acute setting. Children with febrile seizure do not have a higher rate of urinary tract infection compared with other children with fever [24]. Decisions regarding urinalysis and urine cultures should be based solely on factors such as age, sex, and other features in accordance with current urinary tract infection screening recommendations [25].

In published ED data, the fever source is undetermined in most patients [13,18] and, as viral studies are not routinely done, it is unclear to what proportion implicated viruses (influenza [26], and human herpesvirus 6 and 7 [27–29]) are responsible

for the associated febrile illness. Otitis media is the most commonly identified infection [13,14].

Neuroimaging

When imaging is obtained for either simple FS or CFS, emergent findings are very rare [30,31], and the most common MRI abnormalities are subcortical focal hyperintensity, abnormal white matter signal, and focal cortical dysplasia [32▪,33]. The AAP does not recommend routine neuroimaging for children with first simple febrile seizure [34,35].

Hippocampal injury (hippocampal edema and subsequent mesial temporal sclerosis) can occasionally occur during prolonged [36] and focal febrile seizures in infants who otherwise appear normal. Such lesions may increase the risk of focal and prolonged seizures, which in turn may result in more hippocampal lesions. There are no current guidelines regarding imaging with CFS.

Electroencephalography

EEG is of limited value in the evaluation of febrile seizure; although abnormalities may be present in these children, their clinical significance is unclear in predicting febrile seizure recurrence or development of epilepsy [37–39]. Intuitively, epileptiform discharges on the EEGs of patients with febrile seizure are important predictive risk factors for the development of epilepsy as the febrile illness lowers the seizure threshold. Studies suggest that frontal paroxysmal EEG abnormalities are associated with higher risk of epilepsy [37,39], but the frequency of EEG abnormalities in febrile seizure patients is still unclear. The prevalence reported ranges from 2 to 86% [40,41] as a result of varying study populations in terms of age, definition of EEG abnormalities, and the time interval prior to the EEG. Although patients with CFS are more likely to develop epilepsy, it is unclear whether EEG abnormalities are predictive of epilepsy [38]. Performing EEG within 24 h of presentation can show generalized background slowing, which could make identifying possible epileptiform abnormalities difficult [42]. Generalized slowing on EEG can be present up to 7 days after a child presents with febrile status epilepticus [43,44].

The AAP consensus guideline states that an EEG should not be a part of the routine evaluation in neurologically healthy children with a simple febrile seizure [34]. There are no clear recommendations regarding CFS.

BEYOND THE ACUTE SETTING

The first febrile seizure is an overwhelming experience for parents [45▪]. There is a discordance between being rushed to a hospital in an ambulance, and at times transferred to a tertiary pediatric center, and the current state of minimal diagnostic evaluation [46]. Upon discharge, many questions need to be answered about a child's health status, ranging from risk of recurrence, risk of epilepsy, and addressing vaccinations to medical management around the next febrile illness. The next section reviews some of the current knowledge useful to answer these questions.

Risk factors for recurrence

A second episode of febrile seizure will occur in a third of the children with first febrile seizure, and about 10% will experience three or more febrile seizures [47]. Risk factors include family history of febrile seizure, age of onset $<$18 months of age, lower peak temperature, and short duration of fever prior to seizure occurrence [5,47,48]. Multiple risk factors may drive the risk higher. Family history of epilepsy does not predict recurrence of FS, neither do neurodevelopmental abnormalities or a child's sex [49]. To date, the well established risk factors for recurrence (and even early recurrence [50] within 24 h) have not been incorporated in published guidelines addressing rectal diazepam prescription practice. The only consistent practice involves prolonged seizures [49], as a recurrent febrile seizure is also more likely to be prolonged if the initial febrile seizure was prolonged.

Risk factors for subsequent epilepsy

Rate of epilepsy among children with simple febrile seizure is close to the overall rate in the general population. A higher risk (some quantify it as up to 7% [51]) exists in children with a family history of epilepsy, those with CFS, children with recurrence of simple febrile seizure under the age of 12 months (and possibly those older than 3 years of age [52▪]), and those having a short duration of fever prior to seizing. The latter is also a predictor of febrile seizure recurrence. The effect of number of complex features in a febrile seizure on further development of epilepsy is controversial. Within CFS, febrile status epilepticus is associated with epilepsy.

Prophylaxis/medical treatment

Prevention or prophylaxis of febrile seizure involves three main options: vigorous fever management, management of a seizure once it occurs, intermittent use of antiepileptic drugs (AEDs) during a febrile illness, and maintenance AEDs throughout high-risk years [53▪].

Vigorous fever management

Intuitively, managing fever with antipyretics (acetaminophen and/or ibuprofen) may address both temperature height and rapid temperature changes, thus reducing the frequency of febrile seizures. Recent systematic review [54▪▪] of all randomized control trials between 1950 and 2011 showed a febrile seizure recurrence rate of 22.7% among children receiving antipyretics vs. 24.2% in the placebo groups. This strategy is not only ineffective, it adds to parental anxiety by obsessively measuring the child's temperature and to their sense of frustration when seizures occur at or preceding the first noted temperature spike. Antipyretics should therefore be administered to control symptoms related to fever alone.

Immediate management

Using an AED for early termination of seizures may prevent prolonged seizures and neuronal loss. First line of ED treatment involves benzodiazepines (most commonly intravenous lorazepam, 0.1 mg/kg) or diazepam (0.2 mg/kg), which are highly efficacious if given early in the course of a seizure. Contrary to prior beliefs that lorazepam may be superior to diazepam, a recently published randomized control trial showed no difference between these two medications in stopping seizures [55].

In the USA, rectal diazepam (0.5 mg/kg) is the most commonly used medication for out-of-hospital use; however, buccal [56] (0.4 mg/kg) or intranasal [57] (0.2 mg/kg) midazolam is equally effective and well tolerated in stopping an ongoing seizure. Other than patients who experience febrile status epilepticus, clear guidelines for who should be discharged home with a 'rescue' AED are lacking. Factors such as duration, number of seizures, parental preference, and the ability to handle the apneic phase that may follow administration of a benzodiazepine must be considered, prior to prescribing a 'rescue' benzodiazepine.

Intermittent antiepileptic drug therapy at the time of fever

Intermittent diazepam given during febrile illnesses has been clinically proven to reduce the recurrence of both simple and CFS [58]; however, there is a high overall failure rate in preventing febrile seizure as so many precedes the detection of fever. As a result, this practice is discouraged by the AAP. Some, however, advocate its use among the subgroup of patients who had a prolonged febrile seizure [59▪]. Other intermittent AEDs previously studied (such as phenobarbital [60] or valproate [61]) may be effective if given at the onset of fever but are equally discouraged.

Continuous antiepileptic drug therapy

Phenobarbital or valproate (both proven effective in preventing recurrent febrile seizure) is rarely used to prevent febrile seizure. The rate of adverse reactions associated with these anticonvulsants is generally considered to clearly outweigh the risks associated with potential febrile seizure [62].

Other drugs have also been studied. Carbamazepine and phenytoin have limited or no effect on the recurrence of febrile seizure [63]. Levetiracetam may prove to be an effective medication in preventing the recurrence of CFS; however, larger studies are needed.

In summary, medical treatment to affect the natural course of febrile seizure is of limited value. Efforts are focused on preventing febrile status epilepticus. For those parents insisting on medical treatment for simple febrile seizure, rectal diazepam should be considered or intermittent oral diazepam should be considered during illness [46].

Vaccination and febrile seizure

Vaccine-induced febrile seizures are defined as febrile seizure occurring within 72 h of vaccination, although in the case of measles, mumps, and rubella (MMR) vaccine both fever and febrile seizure may be expected between 7 and 14 days. Independent of fever, the risk of febrile seizure also depends on the vaccine type [64,65], with higher rates with MMR, and toxin-containing or whole-cell preparations such as diphtheria–tetanus–acellular pertussis (DTaP) [66], although there is accumulating data that even MMR-associated febrile seizure is genetically mediated [67▪▪]. The practice of delaying MMR vaccines until a child is slightly older should be discouraged as data shows a higher rate of postvaccination seizures for those for whom vaccines were delayed [68▪]. Simultaneous administration of vaccines may also affect the rate of vaccine-associated febrile seizure. This has been reported when influenza and pneumococcal vaccines were given in combination [69] and for recombinant meningococcal serotype B vaccine given with other routine vaccines [DTaP–inactivated polio vaccine–hepatitis B virus/*Haemophilus influenzae* type B (DTaP–IPV–HBV/Hib) and pneumococcal conjugate vaccine (PCV7)] [70▪]. In the latter case, postvaccination fever rate was increased by 70% compared after giving these vaccines separately.

Considerations

ABM, measles, and polio are now rare in the age groups affected by febrile seizure in the USA [71–73] thanks to effective vaccines. Clinicians caring for children with febrile seizure should clearly state the

importance of the prevention of the significant neurologic morbidity associated with these diseases whenever discussing the risk of fever and febrile seizure associated with vaccinations [45▪,65]. To provide reassurance and possibly improve vaccination compliance, one should consider round-the-clock antipyretics after DTaP to reduce postvaccination fever (this is an exception regarding the prior discussion on antipyretics [74]), and for selected patients, oral diazepam may be considered for 1 day following vaccination; a history of febrile seizure (and especially prolonged febrile seizure) should be a relative indication for administration of vaccines at separate visits rather than more than one vaccine at a time.

CONCLUSION

Pediatricians are facing new challenges in managing febrile seizure and advising families: routine diagnostic tests for simple febrile seizure are being discouraged, and their utility for complex febrile seizure is quite poor, leaving clinical acumen as the only tool in identifying children with febrile seizure who are candidates for a more elaborate diagnostic evaluation; prevention of further febrile seizure is challenging, with new evidence showing no effect to control fever; postvaccination febrile seizure may hinder vaccination compliance, and strategies need to be put in place; evidence-based guidelines regarding CFS and identifying candidates for emergent out-of-hospital diazepam treatment are still lacking.

Acknowledgements

We would like to thank Assaf Landschaft, MSc, for his assistance with the study.

Financial support and sponsorship

None.

Conflicts of interest

None of the authors have any conflicts of interest to declare.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Steering Committee on Quality Improvement and Management; Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics 2008; 121:1281–1286.
2. Freeman JM. Febrile seizures: a consensus of their significance, evaluation, and treatment. Pediatrics 1980; 66:1009.
3. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 1993; 34:592–596.
4. Livingston S, Pauli LL, Pruce I, Kramer II. Febrile convulsions: diagnosis, treatment, and prognosis. Pediatr Ann 1979; 8:133–153.
5. Berg AT, Shinnar S. Complex febrile seizures. Epilepsia 1996; 37:126–133.
6. Stafstrom CE. The incidence and prevalence of febrile seizures. San Diego: Academic Press; 2002.
7. Paul SP, Blaikley S, Chinthapalli R. Clinical update: febrile convulsion in childhood. Community Pract 2012; 85:36–38; Accessed 11 June 2014.
8. Baram TZ, Shinnar S. Febrile seizures. San Diego: Academic Press; 2002. http://www.columbia.edu/cgi-bin/cul/resolve?clio10562093. Accessed 11 June 2014.
9. Saghazadeh A, Mastrangelo M, Rezaei N. Genetic background of febrile seizures. Rev Neurosci 2014; 25:129–161.
10. ▪ Ackerson BK, Sy LS, Yao JF, *et al.* Agreement between medical record and parent report for evaluation of childhood febrile seizures. Vaccine 2013; 31:2904–2909.

This manuscript suggests a poor κ between variables recorded in medical records and parental reports.

11. Nigrovic LE, Kuppermann N, Macias CG, *et al.* Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. JAMA 2007; 297:52–60.
12. Green SM, Rothrock SG, Clem KJ, *et al.* Can seizures be the sole manifestation of meningitis in febrile children? Pediatrics 1993; 92:527–534.
13. Kimia A, Ben-Joseph EP, Rudloe T, *et al.* Yield of lumbar puncture among children who present with their first complex febrile seizure. Pediatrics 2010; 126:62–69.
14. Kimia AA, Capraro AJ, Hummel D, *et al.* Utility of lumbar puncture for first simple febrile seizure among children 6 to 18 months of age. Pediatrics 2009; 123:6–12.
15. Seltz LB, Cohen E, Weinstein M. Risk of bacterial or herpes simplex virus meningitis/encephalitis in children with complex febrile seizures. Pediatr Emerg Care 2009; 25:494–497.
16. Watemberg N, Sarouk I, Fainmesser P. Acute meningitis among infants and toddlers with febrile seizures: time for a reappraisal of the value of a lumbar puncture. Isr Med Assoc J 2012; 14:547–549.
17. ▪ Fletcher EM, Sharieff G. Necessity of lumbar puncture in patients presenting with new onset complex febrile seizures. West J Emerg Med 2013; 14:206–211.

Another piece of evidence to show low yield for lumbar puncture among children with complex febrile seizures.

18. Batra P, Gupta S, Gomber S, Saha A. Predictors of meningitis in children presenting with first febrile seizures. Pediatr Neurol 2011; 44:35–39.
19. Chamberlain JM, Gorman RL. Occult bacteremia in children with simple febrile seizures. Am J Dis Child 1988; 142:1073–1076.
20. Teach SJ, Geil PA. Incidence of bacteremia, urinary tract infections, and unsuspected bacterial meningitis in children with febrile seizures. Pediatr Emerg Care 1999; 15:9–12.
21. Trainor JL, Hampers LC, Krug SE, Listernick R. Children with first-time simple febrile seizures are at low risk of serious bacterial illness. Acad Emerg Med 2001; 8:781–787.
22. ▪ Maksikharin A, Prommalikit O. Serum sodium levels do not predict recurrence of febrile seizures within 24 hours. Paediatr Int Child Health 2015; 35:44–46.

A manuscript suggesting limited predictive value for serum sodium, in terms of early seizure recurrence among children with febrile seizures.

23. King D, King A. Question 2: should children who have a febrile seizure be screened for iron deficiency? Arch Dis Child 2014; 99:960–964.
24. Teach SJ, Geil PA. Incidence of bacteremia, urinary tract infections, and unsuspected bacterial meningitis in children with febrile seizures. Pediatr Emerg Care 1999; 15:9–12.
25. Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011; 128:595–610.
26. Chiu SS, Tse CY, Lau YL, Peiris M. Influenza A infection is an important cause of febrile seizures. Pediatrics 2001; 108:E63.
27. Barone SR, Kaplan MH, Krilov LR. Human herpesvirus-6 infection in children with first febrile seizures. J Pediatr V 127 1995; 95–97.
28. Epstein LG, Shinnar S, Hesdorffer DC, *et al.* Human herpesvirus 6 and 7 in febrile status epilepticus: the FEBSTAT study. Epilepsia 2012; 53:1481–1488.
29. Teach SJ, Wallace HL, Evans MJ, *et al.* Human herpesviruses types 6 and 7 and febrile seizures. Pediatr Neurol 1999; 21:699–703.
30. Kimia AA, Ben-Joseph E, Prabhu S, *et al.* Yield of emergent neuroimaging among children presenting with a first complex febrile seizure. Pediatr Emerg Care 2012; 28:316–321.
31. Teng D, Dayan P, Tyler S, *et al.* Risk of intracranial pathologic conditions requiring emergency intervention after a first complex febrile seizure episode among children. Pediatrics 2006; 117:304–308.
32. ▪ Scott RC. What are the effects of prolonged seizures in the brain? Epileptic Disord 2014; 16 (Suppl 1):6–11.

An important overview of the way brain injury occurs during prolonged seizures and a reminder about the importance of early intervention at seizure onset.

33. Scott RC. Consequences of febrile seizures in childhood. Curr Opin Pediatr 2014; 26:662–667.

34. Subcommittee on Febrile Seizures; American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics 2011; 127:389–394.

35. 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; 97:769–772.

36. Lewis DV, Shinnar S, Hesdorffer DC, *et al.* Hippocampal sclerosis after febrile status epilepticus: the FEBSTAT study. Ann Neurol 2014; 75:178–185.

37. Kuang YQ, Kong B, Yang T, *et al.* Epileptiform discharges and frontal paroxysmal EEG abnormality act as predictive marker for subsequent epilepsy in children with complex febrile seizures. Clin EEG Neurosci 2014. [Epub ahead of print] ISSN 1550-0594, http://www.ncbi.nlm.nih.gov/pubmed/24586108.

38. Shah PB, James S, Elayaraja S. EEG for children with complex febrile seizures. Cochrane Database Syst Rev 2014; 1:CD009196.

39. Wo SB, Lee JH, Lee YJ, *et al.* Risk for developing epilepsy and epileptiform discharges on EEG in patients with febrile seizures. Brain Dev 2013; 35:307–311.

40. Kanemura H, Mizorogi S, Aoyagi K, *et al.* EEG characteristics predict subsequent epilepsy in children with febrile seizure. Brain Dev 2012; 34:302–307.

41. Sofijanov N, Emoto S, Kuturec M, *et al.* Febrile seizures: clinical characteristics and initial EEG. Epilepsia 1992; 33:52–57.

42. Yucel O, Aka S, Yazicioglu L, Ceran O. Role of early EEG and neuroimaging in determination of prognosis in children with complex febrile seizure. Pediatr Int 2004; 46:463–467.

43. Nordli DR, Moshe SL, Shinnar S. The role of EEG in febrile status epilepticus (FSE). Brain Dev 2010; 32:37–41.

44. Patel AD, Vidaurre J. Complex febrile seizures: a practical guide to evaluation and treatment. J Child Neurol 2013; 28:762–767.

45. ■ Kanemura H, Sano F, Mizorogi S, *et al.* Parental thoughts and actions regarding their child's first febrile seizure. Pediatr Int 2013; 55:315–319.

A look into parental concerns and beliefs regarding febrile seizures. An opportunity to provide directed guidance and information.

46. Oluwabusi T, Sood SK. Update on the management of simple febrile seizures: emphasis on minimal intervention. Curr Opin Pediatr 2012; 24:259–265.

47. Berg AT, Shinnar S, Darefsky AS, *et al.* Predictors of recurrent febrile seizures. A prospective cohort study. Arch Pediatr Adolesc Med 1997; 151:371–378.

48. 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; 124:574–584.

49. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol Jan 2002; 17 (Suppl 1):S44–S52.

50. Jeong JH, Lee JH, Kim K, *et al.* Rate of and risk factors for early recurrence in patients with febrile seizures. Pediatr Emerg Care 2014; 30:540–545.

51. Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: short-term outcome. Neurology 1996; 47:562–568.

52. ■ Pavlidou E, Panteliadis C. Prognostic factors for subsequent epilepsy in children with febrile seizures. Epilepsia 2013; 54:2101–2107.

Great piece of data added to the body of evidence regarding risk of epilepsy among children with febrile seizure.

53. ■ Offringa M, Newton R. Prophylactic drug management for febrile seizures in children (Review). Evid Based Child Health 2013; 8:1376–1485.

An outstanding review, addressing options, pros and cons, or medical prophylaxis attempt of febrile seizure.

54. ■■ Rosenbloom E, Finkelstein Y, Adams-Webber T, Kozer E. Do antipyretics prevent the recurrence of febrile seizures in children? A systematic review of randomized controlled trials and meta-analysis. Eur J Paediatr Neurol 2013; 17:585–588.

A key piece of evidence addressing the false belief that strict fever management will prevent febrile seizure.

55. Chamberlain JM, Okada P, Holsti M, *et al.* Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA 2014; 311:1652–1660.

56. 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; 366:205–210.

57. Holsti M, Dudley N, Schunk J, *et al.* Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. Arch Pediatr Adolesc Med 2010; 164:747–753.

58. Autret E, Billard C, Bertrand P, *et al.* Double-blind, randomized trial of diazepam versus placebo for prevention of recurrence of febrile seizures. J Pediatr 1990; 117:490–494.

59. ■ Camfield P, Camfield C. Are febrile seizures an indication for intermittent benzodiazepine treatment, and if so, in which cases? Epileptic Disord 2014. [Epub ahead of print] ISSN 1294-9361, http://www.ncbi.nlm.nih.gov/pubmed/25299426.

Evidence of febrile seizure prophylaxis.

60. Wolf SM. Effectiveness of daily phenobarbital in the prevention of febrile seizure recurrences in 'simple' febrile convulsions and 'epilepsy triggered by fever'. Epilepsia 1977; 18:95–99.

61. Wallace SJ, Smith JA. Successful prophylaxis against febrile convulsions with valproic acid or phenobarbitone. Br Med J 1980; 280:353–354.

62. Herranz JL, Armijo JA, Arteaga R. Effectiveness and toxicity of phenobarbital, primidone, and sodium valproate in the prevention of febrile convulsions, controlled by plasma levels. Epilepsia 1984; 25:89–95.

63. Baumann RJ, Duffner PK. Treatment of children with simple febrile seizures: the AAP practice parameter. American Academy of Pediatrics. Pediatr Neurol 2000; 23:11–17.

64. Macartney KK, Gidding HF, Trinh L, *et al.* Febrile seizures following measles and varicella vaccines in young children in Australia. Vaccine 2015; 33:1412–1417.

65. Brown NJ, Berkovic SF, Scheffer IE. Vaccination, seizures and 'vaccine damage'. Curr Opin Neurol 2007; 20:181–187.

66. Braun MM, Mootrey GT, Salive ME, *et al.* Infant immunization with acellular pertussis vaccines in the United States: assessment of the first two years' data from the Vaccine Adverse Event Reporting System (VAERS). Pediatrics 2000; 106:E51.

67. ■■ Feenstra B, Pasternak B, Geller F, *et al.* Common variants associated with general and MMR vaccine-related febrile seizures. Nat Genet 2014; 46:1274–1282.

Data suggesting that even vaccine-mediated febrile seizure have a genetic basis.

68. ■ Feemster KA. Delay in measles vaccination is associated with increased risk of postvaccination seizures. J Pediatr 2014; 164:674.

Important evidence arguing against the practice of delaying MMR vaccination.

69. Principi N, Esposito S. Vaccines and febrile seizures. Expert Rev Vaccines 2013; 12:885–892.

70. ■ Vesikari T, Esposito S, Prymula R, *et al.* Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. Lancet 2013; 381:825–835.

Data to support safer vaccination practice in terms of postvaccination febrile seizure occurrence.

71. Lee GM, Harper MB. Risk of bacteremia for febrile young children in the post-*Haemophilus influenzae* type b era. Arch Pediatr Adolesc Med 1998; 152:624–628.

72. Barlow WE, Davis RL, Glasser JW, *et al.* The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001; 345:656–661.

73. Dagan R. Immunisation with a pneumococcal 7-valent conjugate vaccine. Int J Clin Pract 2002; 56:287–291.

74. Kohl KS, Marcy SM, Blum M, *et al.* Fever after immunization: current concepts and improved future scientific understanding. Clin Infect Dis 2004; 39:389–394.