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Febrile Seizures: Clinical Practice Guideline for the Long-term Management of the Child With Simple Febrile Seizures

Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures

Pediatrics 2008;121;1281
DOI: 10.1542/peds.2008-0939

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CLINICAL PRACTICE GUIDELINE

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ABSTRACT

Febrile seizures are the most common seizure disorder in childhood, affecting 2% to 5% of children between the ages of 6 and 60 months. Simple febrile seizures are defined as brief (<15-minute) generalized seizures that occur once during a 24-hour period in a febrile child who does not have an intracranial infection, metabolic disturbance, or history of afebrile seizures. This guideline (a revision of the 1999 American Academy of Pediatrics practice parameter [now termed clinical practice guideline] "The Long-term Treatment of the Child With Simple Febrile Seizures") addresses the risks and benefits of both continuous and intermittent anticonvulsant therapy as well as the use of antipyretics in children with simple febrile seizures. It is designed to assist pediatricians by providing an analytic framework for decisions regarding possible therapeutic interventions in this patient population. It is not intended to replace clinical judgment or to establish a protocol for all patients with this disorder. Rarely will these guidelines be the only approach to this problem. *Pediatrics* 2008;121:1281–1286

www.pediatrics.org/cgi/doi/10.1542/peds.2008-0939

doi:10.1542/peds.2008-0939

Key Word
fever

Abbreviation
AAP—American Academy of Pediatrics

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

The expected outcomes of this practice guideline include:

1. optimizing practitioner understanding of the scientific basis for using or avoiding various proposed treatments for children with simple febrile seizures;
2. improving the health of children with simple febrile seizures by avoiding therapies with high potential for adverse effects and no demonstrated ability to improve children's long-term outcomes;
3. reducing costs by avoiding therapies that will not demonstrably improve children's long-term outcomes; and
4. helping the practitioner educate caregivers about the low risks associated with simple febrile seizures.

The committee determined that with the exception of a high rate of recurrence, no long-term effects of simple febrile seizures have been identified. The risk of developing epilepsy in these patients is extremely low, although slightly higher than that in the general population. No data, however, suggest that prophylactic treatment of children with simple febrile seizures would reduce the risk, because epilepsy likely is the result of genetic predisposition rather than structural damage to the brain caused by recurrent simple febrile seizures. Although antipyretics have been shown to be ineffective in preventing recurrent febrile seizures, there is evidence that continuous anticonvulsant therapy with phenobarbital, primidone, or valproic acid and intermittent therapy with diazepam are effective in reducing febrile-seizure recurrence. The potential toxicities associated with these agents, however, outweigh the relatively minor risks associated with simple febrile seizures. As such, the committee concluded that, on the basis of the risks and benefits of the effective therapies, neither continuous nor intermittent anticonvulsant therapy is recommended for children with 1 or more simple febrile seizures.

INTRODUCTION

Febrile seizures are seizures that occur in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures. Febrile seizures are subdivided into 2 categories: simple and complex. Simple febrile seizures last for less than 15 minutes, are generalized (without a focal component), and occur once in a 24-hour period, whereas complex febrile seizures are prolonged (>15 minutes), are focal, or occur more than once in 24 hours.[1] Despite the frequency of febrile seizures (2%–5%), there is no unanimity of opinion about management options. This clinical practice guideline addresses potential therapeutic interventions in neurologically normal children with simple febrile seizures. It is not intended for patients with complex febrile seizures and does not pertain to children with previous neurologic insults, known central nervous system abnor-

malities, or a history of afebrile seizures. This clinical practice guideline is a revision of a 1999 American Academy of Pediatrics (AAP) clinical practice parameter, "The Long-term Treatment of the Child With Simple Febrile Seizures."[2]

For a child who has experienced a simple febrile seizure, there are potentially 4 adverse outcomes that theoretically may be altered by an effective therapeutic agent: (1) decline in IQ; (2) increased risk of epilepsy; (3) risk of recurrent febrile seizures; and (4) death. Neither a decline in IQ, academic performance or neurocognitive inattention nor behavioral abnormalities have been shown to be a consequence of recurrent simple febrile seizures.[3] Ellenberg and Nelson[4] studied 431 children who experienced febrile seizures and observed no significant difference in their learning compared with sibling controls. In a similar study by Verity et al,[5] 303 children with febrile seizures were compared with control children. No difference in learning was identified, except in those children who had neurologic abnormalities before their first seizure.

The second concern, increased risk of epilepsy, is more complex. Children with simple febrile seizures have approximately the same risk of developing epilepsy by the age of 7 years as does the general population (ie, 1%).[6] However, children who have had multiple simple febrile seizures, are younger than 12 months at the time of their first febrile seizure, and have a family history of epilepsy are at higher risk, with generalized afebrile seizures developing by 25 years of age in 2.4%.[7] Despite this fact, no study has demonstrated that successful treatment of simple febrile seizures can prevent this later development of epilepsy, and there currently is no evidence that simple febrile seizures cause structural damage to the brain. Indeed, it is most likely that the increased risk of epilepsy in this population is the result of genetic predisposition.

In contrast to the slightly increased risk of developing epilepsy, children with simple febrile seizures have a high rate of recurrence. The risk varies with age. Children younger than 12 months at the time of their first simple febrile seizure have an approximately 50% probability of having recurrent febrile seizures. Children older than 12 months at the time of their first event have an approximately 30% probability of a second febrile seizure; of those who do have a second febrile seizure, 50% have a chance of having at least 1 additional recurrence.[8]

Finally, there is a theoretical risk of a child dying during a simple febrile seizure as a result of documented injury, aspiration, or cardiac arrhythmia, but to the committee's knowledge, it has never been reported.

In summary, with the exception of a high rate of recurrence, no long-term adverse effects of simple febrile seizures have been identified. Because the risks associated with simple febrile seizures, other than recurrence, are so low and because the number of children who have febrile seizures in the first few years of life is so high, to be commensurate, a proposed therapy would need to be exceedingly low in risks and adverse effects, inexpensive, and highly effective.

METHODS

To update the clinical practice guideline on the treatment of children with simple febrile seizures, the AAP reconvened the Subcommittee on Febrile Seizures. The committee was chaired by a child neurologist and consisted of a neuroepidemiologist, 2 additional child neurologists, and a practicing pediatrician. All panel members reviewed and signed the AAP voluntary disclosure and conflict-of-interest form. The guideline was reviewed by members of the AAP Steering Committee on Quality Improvement and Management; members of the AAP Sections on Neurology, Pediatric Emergency Medicine, Developmental and Behavioral Pediatrics, and Epidemiology; members of the AAP Committees on Pediatric Emergency Medicine and Medical Liability and Risk Management; members of the AAP Councils on Children With Disabilities and Community Pediatrics; and members of outside organizations including the Child Neurology Society and the American Academy of Neurology.

A comprehensive review of the evidence-based literature published since 1998 was conducted with the aim of addressing possible therapeutic interventions in the management of children with simple febrile seizures. The review focused on both the efficacy and potential adverse effects of the proposed treatments. Decisions were made on the basis of a systematic grading of the quality of evidence and strength of recommendations.

The AAP established a partnership with the University of Kentucky (Lexington, KY) to develop an evidence report, which served as a major source of information for these practice-guideline recommendations. The specific issues addressed were (1) effectiveness of continuous anticonvulsant therapy in preventing recurrent febrile seizures, (2) effectiveness of intermittent anticonvulsant therapy in preventing recurrent febrile seizures, (3) effectiveness of antipyretics in preventing recurrent febrile seizures, and (4) adverse effects of either continuous or intermittent anticonvulsant therapy.

In the original practice parameter, more than 300 medical journal articles reporting studies of the natural history of simple febrile seizures or the therapy of these seizures were reviewed and abstracted.[2] An additional 65 articles were reviewed and abstracted for the update. Emphasis was placed on articles that differentiated simple febrile seizures from other types of seizures, that carefully matched treatment and control groups, and that described adherence to the drug regimen. Tables were constructed from the 65 articles that best fit these criteria. A more comprehensive review of the literature on which this report is based can be found in a forthcoming technical report (the initial technical report can be accessed at http://aappolicy.aappublications.org/cgi/content/full/pediatrics;103/6/e86). The technical report also will contain dosing information.

The evidence-based approach to guideline development requires that the evidence in support of a recommendation be identified, appraised, and summarized and that an explicit link between evidence and recommendations be defined. Evidence-based recommendations reflect the quality of evidence and the balance of benefit and harm that is

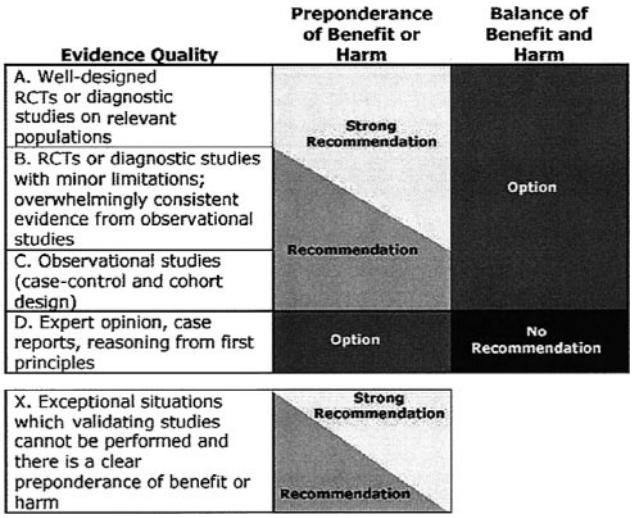

FIGURE 1

Integrating evidence-quality appraisal with an assessment of the anticipated balance between benefits and harms if a policy is conducted leads to designation of a policy as a strong recommendation, recommendation, option, or no recommendation. RCT indicates randomized, controlled trial.

anticipated when the recommendation is followed. The AAP policy statement "Classifying Recommendations for Clinical Practice Guidelines"[9] was followed in designating levels of recommendations (see Fig 1 and Table 1).

RECOMMENDATION

On the basis of the risks and benefits of the effective therapies, neither continuous nor intermittent anticonvulsant therapy is recommended for children with 1 or more simple febrile seizures.

- Aggregate evidence quality: B (randomized, controlled trials and diagnostic studies with minor limitations).
- Benefit: prevention of recurrent febrile seizures, which are not harmful and do not significantly increase the risk for development of future epilepsy.
- Harm: adverse effects including rare fatal hepatotoxicity (especially in children younger than 2 years who are also at greatest risk of febrile seizures), thrombocytopenia, weight loss and gain, gastrointestinal disturbances, and pancreatitis with valproic acid and hyperactivity, irritability, lethargy, sleep disturbances, and hypersensitivity reactions with phenobarbital; lethargy, drowsiness, and ataxia for intermittent diazepam as well as the risk of masking an evolving central nervous system infection.
- Benefits/harms assessment: preponderance of harm over benefit.
- Policy level: recommendation.

BENEFITS AND RISKS OF CONTINUOUS ANTICONVULSANT THERAPY

Phenobarbital

Phenobarbital is effective in preventing the recurrence of simple febrile seizures.[10] In a controlled double-blind study, daily therapy with phenobarbital reduced the rate of subsequent febrile seizures from 25 per 100 subjects per year to 5 per 100 subjects per year.[11] For the agent to be effective, however, it must be given daily and maintained in the therapeutic range. In a study by Farwell et al,[12] for example, children whose phenobarbital levels were in the therapeutic range had a reduction in recurrent seizures, but because noncompliance was so high, an overall benefit with phenobarbital therapy was not identified.

The adverse effects of phenobarbital include hyperactivity, irritability, lethargy, sleep disturbances, and hypersensitivity reactions. The behavioral adverse effects

TABLE 1 **Guideline Definitions for Evidence-Based Statements**

Statement	Definition	Implication
Strong recommendation	A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high-quality evidence is impossible to obtain but the anticipated benefits outweigh the harms.	Clinicians would be prudent to follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to 1 approach over another.	Clinicians should consider the option in their decision-making, and patient preference may have a substantial role.
No recommendation	No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.	Clinicians should be alert to new published evidence that clarifies the balance of benefit versus harm.

may occur in up to 20% to 40% of patients and may be severe enough to necessitate discontinuation of the drug.[13–16]

Primidone

Primidone, in doses of 15 to 20 mg/kg per day, has also been shown to reduce the recurrence rate of febrile seizures.[17,18] It is of interest that the derived phenobarbital level in a Minigawa and Miura study[17] was below therapeutic (16 μg/mL) in 29 of the 32 children, suggesting that primidone itself may be active in preventing seizure recurrence. As with phenobarbital, adverse effects include behavioral disturbances, irritability, and sleep disturbances.[18]

Valproic Acid

In randomized, controlled studies, only 4% of children taking valproic acid, as opposed to 35% of control subjects, had a subsequent febrile seizure. Therefore, valproic acid seems to be at least as effective in preventing recurrent simple febrile seizures as phenobarbital and significantly more effective than placebo.[19–21]

Drawbacks to therapy with valproic acid include its rare association with fatal hepatotoxicity (especially in children younger than 2 years, who are also at greatest risk of febrile seizures), thrombocytopenia, weight loss and gain, gastrointestinal disturbances, and pancreatitis. In studies in which children received valproic acid to prevent recurrence of febrile seizures, no cases of fatal hepatotoxicity were reported.[15]

Carbamazepine

Carbamazepine has not been shown to be effective in preventing the recurrence of simple febrile seizures. Antony and Hawke[13] compared children who had been treated with therapeutic levels of either phenobarbital or carbamazepine, and 47% of the children in the carbamazepine-treated group had recurrent seizures compared with only 10% of those in the phenobarbital group. In another study, Camfield et al[22] treated children (whose conditions failed to improve with phenobarbital therapy) with carbamazepine. Despite good compliance, 13 of the 16 children treated with carbamazepine had a recurrent febrile seizure within 18 months. It is theoretically possible that these excessively high rates of recurrences might have been attributable to adverse effects of carbamazepine.

Phenytoin

Phenytoin has not been shown to be effective in preventing the recurrence of simple febrile seizures, even when the agent is in the therapeutic range.[23,24] Other anticonvulsants have not been studied for the continuous treatment of simple febrile seizures.

BENEFITS AND RISKS OF INTERMITTENT ANTICONVULSANT THERAPY

Diazepam

A double-blind controlled study of patients with a history of febrile seizures demonstrated that administration of oral diazepam (given at the time of fever) could reduce the recurrence of febrile seizures. Children with a history of febrile seizures were given either oral diazepam (0.33 mg/kg, every 8 hours for 48 hours) or a placebo at the time of fever. The risk of febrile seizures per person-year was decreased 44% with diazepam.[25] In a more recent study, children with a history of febrile seizures were given oral diazepam at the time of fever and then compared with children in an untreated control group. In the oral diazepam group, there was an 11% recurrence rate compared with a 30% recurrence rate in the control group.[26] It should be noted that all children for whom diazepam was considered a failure had been noncompliant with drug administration, in part because of adverse effects of the medication.

There is also literature that demonstrates the feasibility and safety of interrupting a simple febrile seizure lasting less than 5 minutes with rectal diazepam and with both intranasal and buccal midazolam.[27,28] Although these agents are effective in terminating the seizure, it is questionable whether they have any long-term influence on outcome. In a study by Knudsen et al,[29] children were given either rectal diazepam at the time of fever or only at the onset of seizure. Twelve-year follow-up found that the long-term prognosis of the children in the 2 groups did not differ regardless of whether treatment was aimed at preventing seizures or treating them.

A potential drawback to intermittent medication is that a seizure could occur before a fever is noticed. Indeed, in several of these studies, recurrent seizures were likely attributable to failure of method rather than failure of the agent.

Adverse effects of oral and rectal diazepam[26] and both intranasal and buccal midazolam include lethargy, drowsiness, and ataxia. Respiratory depression is extremely rare, even when given by the rectal route.[28,30] Sedation caused by any of the benzodiazepines, whether administered by the oral, rectal, nasal, or buccal route, have the potential of masking an evolving central nervous system infection. If used, the child's health care professional should be contacted.

BENEFITS AND RISKS OF INTERMITTENT ANTIPYRETICS

No studies have demonstrated that antipyretics, in the absence of anticonvulsants, reduce the recurrence risk of simple febrile seizures. Camfield et al[11] treated 79 children who had had a first febrile seizure with either a placebo plus antipyretic instruction (either aspirin or acetaminophen) versus daily phenobarbital plus antipyretic instruction (either aspirin or acetaminophen). Recurrence risk was significantly lower in the phenobarbital-treated group, suggesting that antipyretic instruction, including the use of antipyretics, is ineffective in preventing febrile-seizure recurrence.

Whether antipyretics are given regularly (every 4 hours) or sporadically (contingent on a specific body-temperature elevation) does not influence outcome. Acetaminophen was either given every 4 hours or only for temperature elevations of more than 37.9°C in 104 children. The incidence of febrile episodes did not differ

significantly between the 2 groups, nor did the early recurrence of febrile seizures. The authors determined that administering prophylactic acetaminophen during febrile episodes was ineffective in preventing or reducing fever and in preventing febrile-seizure recurrence.[31]

In a randomized double-blind placebo-controlled trial, acetaminophen was administered along with low-dose oral diazepam.[32] Febrile-seizure recurrence was not reduced, compared with control groups. As with acetaminophen, ibuprofen also has been shown to be ineffective in preventing recurrence of febrile seizures.[33–35]

In general, acetaminophen and ibuprofen are considered to be safe and effective antipyretics for children. However, hepatotoxicity (with acetaminophen) and respiratory failure, metabolic acidosis, renal failure, and coma (with ibuprofen) have been reported in children after overdose or in the presence of risk factors.[36,37]

CONCLUSIONS

The subcommittee has determined that a simple febrile seizure is a benign and common event in children between the ages of 6 and 60 months. Nearly all children have an excellent prognosis. The committee concluded that although there is evidence that both continuous antiepileptic therapy with phenobarbital, primidone, or valproic acid and intermittent therapy with oral diazepam are effective in reducing the risk of recurrence, the potential toxicities associated with antiepileptic drugs outweigh the relatively minor risks associated with simple febrile seizures. As such, long-term therapy is not recommended. In situations in which parental anxiety associated with febrile seizures is severe, intermittent oral diazepam at the onset of febrile illness may be effective in preventing recurrence. Although antipyretics may improve the comfort of the child, they will not prevent febrile seizures.

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Pediatrics 2008;121;1281
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