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Are febrile seizures an indication for intermittent benzodiazepine treatment, and if so, in which cases?

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ABSTRACT – Febrile seizures occur in ~4% of children. After a first febrile seizure, the risk of recurrence is ~40%, but excellent studies document that febrile seizures do not cause brain damage or deficits in cognition or behaviour. The risk of subsequent epilepsy is 2-4%. Prolonged febrile seizures are of concern because a child may later develop mesial temporal sclerosis and intractable epilepsy in rare cases. Most prolonged febrile seizures represent the first febrile seizure and cannot be anticipated. A first prolonged febrile seizure does not increase the risk of recurrence, but if there is a recurrence, it is more likely to be prolonged. Prevention of recurrent febrile seizures is difficult. Antipyretics are ineffective. Daily AED treatment is not often justified. Intermittent oral diazepam at the time of illness is not very successful and has significant side effects. The most optimistic study found that the number of subjects required to treat in order to prevent one recurrence was 14. Intermittent clobazam has fewer side effects than diazepam and may be somewhat effective. Rescue benzodiazepines given outside health care facilities may be effective in selected patients to prevent prolonged recurrences, although this has not been proven with rectal diazepam which has been more extensively studied than buccal or nasal midazolam. Currently, we suggest that, for children with febrile seizures, candidates for consideration for rescue benzodiazepines are those with a prolonged febrile seizure or poor access to medical care. It is possible that the use of a rescue benzodiazepine may alleviate severe parental anxiety, but this remains to be established.

Key words: febrile seizure, recurrent seizure, prolonged, benzodiazepine

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Febrile seizures represent by far the most common convulsive event in humans. From birth to death, everyone faces, on average, an 8% risk of having some form of seizure and half of this risk corresponds to the chance of having a febrile seizure (Hauser and Kurland, 1975). Based on an overwhelming amount of evidence, primarily from population-based studies from various countries, the basic facts about febrile seizures are well-known (Nelson and Ellenberg, 1976; Verity *et al*., 1998; Annegers *et al*., 1987). About 3-6% of the population will

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have at least one febrile seizure at a peak age of 18 months, over a typical range of 4 months to 5 years. Children will occasionally have a febrile seizure at an older age. After a first febrile seizure, ~40% will have a recurrence. Few children will have three or more recurrences. Febrile seizures do not cause brain injury and are not associated with cognitive, personality, or behavioural changes. Specific issues concerning prolonged febrile seizures are discussed below. Children with "simple" febrile seizures have a 2-3% chance of later developing epilepsy. Those with complex febrile seizures (focal, prolonged, or repeated in the same illness) have a slightly increased risk (5-13%), but still, the vast majority do not develop epilepsy (Nelson and Ellenberg, 1976; Annegers *et al*., 1987).

On the other hand, several studies have shown that epilepsy in children is preceded by febrile seizures in ~15%, regardless of the epilepsy syndrome or the cause (Sofijanov, 1982; Camfield *et al*., 1994). This suggests that febrile seizures do not cause epilepsy, but rather, that the genes that determine the febrile seizure tendency are very important in determining a person's seizure threshold.

For this review, it is extremely important to realise that most, perhaps two thirds, of prolonged febrile seizures represent the first febrile seizure and that there is no way to anticipate them (Nelson and Ellenberg, 1976; Berg and Shinnar, 1996; Hesdorffer *et al*., 2013). Prolonged febrile seizures are of concern because of the observed sequence of a prolonged febrile seizure followed by intractable temporal lobe epilepsy caused by mesial temporal sclerosis. This sequence is relatively rare and has been estimated to occur in 1-2/150,000 children (Camfield *et al*., 1994). Following a very prolonged febrile seizure (most cases are longer that an hour), a recent study of 191 patients found that 10% showed mesial temporal T2 changes on MRI within 72 hours of their seizure, although we still do not know how many of these patients will develop MTS, temporal lobe epilepsy, or intractable temporal lobe epilepsy (Shinnar *et al*., 2012). The same MRI study showed that children with very prolonged febrile seizures also had an increased risk of partially malrotated hippocampus, a minor developmental anomaly. Interestingly, the malrotation was most often not on the same side as the T2 MRI changes.

The final concern for brain injury from febrile seizures is the hemiconvulsion-hemiplegia-epilepsy syndrome. Here, an extremely prolonged focal febrile seizure lasting hours is followed by permanent hemiplegia, contralateral brain hemiatrophy, and epilepsy (Tenney and Schapiro, 2012). This disastrous sequence has nearly vanished in developed countries, presumably as the result of aggressive treatment of status epilepticus.

There is no doubt that a major problem of febrile seizures is the upset they cause to parents. In studies from several countries, a very high proportion of parents from many different cultures reported that they thought their child was dying during their first febrile seizure (Balslev, 1991; Kolahi and Tahmooreszadeh, 2009). Understandably, parents are anxious about further illnesses. The effectiveness of education to allay these fears has not been well studied.

Prevention of recurrent febrile seizures

Effective treatment to prevent recurrent febrile seizures has been elusive. Some of the issues are outlined in *table 1*. Remarkably, there is no benefit from aggressive antipyretic treatment at the time of illness (Offringa and Newton, 2013). Appropriate doses of acetaminophen, ibuprofen, and diclofenac have all been shown to be ineffective in double-blind trials.

Daily AED treatment seems unjustified, given the benign nature of febrile seizures. Daily phenobarbital, with its attendant behavioural and cognitive side effects, and valproic acid, with its risk of liver failure, may be effective, although several meta-analyses have contested this assertion (Masuko *et al*., 2003; Offringa and Newton, 2013). One meta-analysis suggested that the number of children required to treat with daily phenobarbital in order to prevent one febrile seizure was eight and with valproic acid was four (Rantala *et al*., 1997); carbamazepine and phenytoin appeared to be ineffective. More recent AEDs have simply not been studied. Benzodiazepines given intermittently at the time of illness may have some effect (*see below*).

Intermittent treatment with benzodiazepines

Benzodiazepines can be given at the time of illness to try to prevent recurrence of febrile seizures or at the time of a febrile seizure to limit its duration. Whatever the drug and whatever the route of administration, there are several important caveats to this approach of treatment. First, the drug must be available at all times. This means that carers must have the drug with them at home, in the car, at day-care centres, and anywhere else where they might travel with the child. Second, the number of carers must be relatively small and all carers must be willing to administer the drug; this includes grandparents, babysitters, and day-care workers. At least in North America, for the majority of families, both parents are employed outside the house, so there are nearly always multiple carers for toddlers and preschool children. Third, all of those who might administer the drug must know how to do it accurately. All benzodiazepines have the potential to cause

Table 1. Issues for the treatment of febrile seizures

What should be the goals of treatment for febrile seizures?
1) Since there is some risk of brain injury from extremely prolonged febrile seizures, it would be desirable to prevent or shorten them.
2) Since families are extremely upset by febrile seizures; treatments that reduce this anxiety might be beneficial.
What are untenable goals of treatment?
1) Prevention of subsequent epilepsy
2) Improvement of cognitive outcome
What are the caveats for treatment with intermittent benzodiazepines?
1) Instant availability of the drug
2) Number of carers
3) Willingness of all carers to administer the drug
4) Teaching carers

significant sedation with too large a dose. Fourth, teaching carers about administering the drug should be carried out by health professionals. In our experience with 30 families who were instructed to give liquid rectal diazepam at home for prolonged seizures, we were very concerned to learn that, unbeknownst to us, 12 of the parents taught others how to give the diazepam (Camfield *et al*., 1989). We strongly discourage this practice for fear of overdose.

Approaches to intermittent benzodiazepine treatment

There are two approaches to intermittent benzodiazepine treatment; treatment during illness and treatment once a seizure starts.

Treatment during illness has not been a very effective approach. The best known study involved oral diazepam at 0.33 mg/kg, given every 8 hours during illness (Rosman *et al*., 1993). This study randomised 406 patients with a first febrile seizure to receive oral diazepam or placebo at the time of illness and showed that the chance of a recurrence was marginally statistically reduced. The risk of recurrence was reduced from 31 to 23%. Unfortunately, about 30-40% of children receiving diazepam had significant side effects, including drowsiness and ataxia. These are very concerning symptoms considering their overlap with symptoms of meningitis which is always a concern for a child with a febrile seizure. No data was offered regarding the number of consultations with a physician or emergency room visits for these symptoms. We calculated that this regime would require treatment of 14 patients to prevent a single recurrent febrile seizure (Camfield *et al*., 1995). In the study, some patients took the diazepam exactly as per protocol and yet had a recurrence; oral diazepam is not 100% effective. No benefit was identified based on other randomised trials using a smaller dose of oral diazepam, therefore, reducing the dose to reduce side effects is not likely to be an effective strategy (Autret *et al*., 1990; Uhari *et al*., 1995).

A small, but intriguing, randomised study used oral clobazam (n=20) *versus* placebo (n=19) as an intermittent treatment and found clobazam to be very effective (Rose *et al*., 2005). A second randomised, small study compared intermittent clobazam (n=37) with intermittent diazepam (n=35) and found both drugs to be equally effective in preventing recurrences, but noted that 20 (54%) cases in the diazepam group and 5 (14.2%) in the clobazam group developed drowsiness and sedation (p=0.0001) (Khosroshahi *et al*., 2011). More investigations with intermittent oral clobazam may be warranted.

Given the benign nature of febrile seizures, it is unfortunate that no randomised study has examined the effect on parental anxiety of intermittent, preventative benzodiazepine treatment for their child. Are parents rendered more or less anxious by the need to frequently check the child's temperature and give medication with side effects? Would they be better off with a "grin and bear it" approach. In Nova Scotia, intermittent treatment is rarely offered, but we know that children with febrile seizures do not consume more health care resources than controls, and parents are not constantly rushing to the doctor with their child (Gordon *et al*., 2000).

The other approach is to offer benzodiazepines as "rescue" medication. The basis of this concept is that parents or carers give a dose of benzodiazepine only during an actual recurrent febrile seizure with a view to preventing a prolonged febrile seizure (Knudsen, 1996). This approach is limited to routes of administration with rapid absorption; rectal diazepam, rectal or sublingual lorazepam, or nasal/buccal midazolam. Rectal diazepam and buccal midazolam have been fairly extensively studied in emergency room settings and both are effective at stopping seizures (Rainbow *et al*., 2002). In a relatively recent randomised study of patients with prolonged seizures due to any cause in an emergency department, it appeared that buccal midazolam was superior to rectal diazepam; the first dose of buccal midazolam was successful in 56%, compared to 27% with rectal diazepam (McIntyre *et al*., 2005). There are advantages to buccal midazolam but rectal diazepam has been more systematically studied and it is likely that both are effective, however, both have some failings. Despite the intuitive nature of this treatment with benzodiazepines during a recurrent febrile seizure, there are no data from randomised trials to show a reduction in prolonged febrile seizures. One large case series suggested that rescue rectal diazepam did not completely alleviate parental anxiety (Rossi *et al*., 1989). All of the caveats for intermittent treatment to prevent febrile seizures apply to the approach of rescue medication during an actual seizure, with an extra need to be certain about correct dosing. Sublingual and rectal preparations can produce very high drug serum levels with the possibility of apnoea.

Who might be a candidate for intermittent benzodiazepine treatment?

Intermittent treatment to prevent a recurrence

In our opinion, oral diazepam is not sufficiently effective to be used to try to prevent recurrent febrile seizures. Effective doses mean significant side effects, and the prospect of treating 13 children unnecessarily to prevent a single febrile seizure in the fourteenth child is unpalatable. Oral clobazam needs further study. If oral preventative treatment is to be considered, there are some factors that make a recurrence more likely. These include a family history of febrile seizures, age at first febrile seizure <18 months, temperature at the time of the first febrile seizure <101°F, and a short illness before the seizure (<1 hour). In one prospective study of 428 children with a first febrile seizure, children with none of these four risk factors had a 14% risk of recurrence. With one factor, the risk was 23%, with two factors 32%, with three factors 62%, and with all four 76% (Berg *et al*., 1997). Some, but not all, studies have found that attendance at day-care centres increases the risk of recurrence as the result of increased infections. It is worth noting that these risk factors are quite different to the risk factors for epilepsy following a febrile seizure.

In addition, it is important to realise that a prolonged first febrile seizure does not increase the risk of a recurrent febrile seizure. However, if the first febrile seizure is prolonged (>10 minutes), the chance of a prolonged recurrence (>10 minutes) has been estimated at 20%, compared to a 6.8% risk of a prolonged recurrence if the first seizure was brief (Berg and Shinnar, 1996). This study was based on a prospective assessment of 118 patients with a first and then recurrent febrile seizure. If preventative intermittent therapy is to be considered, then it may make most sense to limit its use to those with three or four risk factors for recurrence. A randomised study of 139 children who received intermittent oral diazepam (0.33 mg/kg) or no benzodiazepines found that the greatest reduction in febrile seizure recurrence was in those at highest risk of recurrence (Pavlidou *et al*., 2006).

Home use of a "rescue" benzodiazepine at the time of a recurrent febrile seizure

Since the most defensible goal of rescue medication is to prevent a prolonged recurrent febrile seizure, it would be very useful to identify who might be at risk. Unfortunately, as noted above, the only predictive factor appears to be a prolonged first febrile seizure. We believe that it is reasonable to offer home buccal midazolam or rectal diazepam to these families, although we emphasize that no study has shown the true value of this approach.

Other families may benefit from this approach, either based on a very itinerate lifestyle or limited access to medical care. For example, we often encounter families who travel with their children during holidays. They seem to gain in self confidence if they have a rescue medication available. Again, this has not been proven. Other families, especially in Canada, live in settings that are many hours travel from medical care. A very prolonged recurrent febrile seizure might be a disaster and therefore home treatment would seem justifiable. For families that are very anxious about febrile seizures, a rescue benzodiazepine may be helpful with all of the caveats mentioned above. The prescribing physician needs to monitor the apparent value of this treatment to be sure that it does not increase anxiety.

Should every family with a child with a first febrile seizure be offered home rescue benzodiazepines? In our opinion (and experience) the vast majority cope quite well and the facts about febrile seizures are so reassuring that more intervention does not seem justified. □

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