Abstract

Although most febrile seizures do no harm and two-thirds of initial cases have no witnessed recurrence, the seizures cause much family anxiety, and are sometimes prolonged. In rare cases they are the first evidence of important epilepsy syndromes or are implicated in the development of epilepsy with mesial temporal sclerosis in later life. There have been trials of prophylactic treatment with antiepileptic drugs including carbamazepine, diazepam, phenobarbital, phenytoin, and sodium valproate. Several strategies have been employed with these drugs, including continuous secondary prophylaxis, intermittent secondary prophylaxis in response to later episodes of fever, and rescue medication early in the course of further seizures. Another treatment strategy has been using one or more antipyretic agents in early response to fever using agents such as acetaminophen and ibuprofen. Over the years, researchers have identified a variety of clinical, genetic, and environmental risk factors for more severe or prolonged febrile seizures and higher risk of recurrence. This review evaluates the rationale for secondary prophylaxis of febrile seizures, the potential effectiveness of such treatment, and whether it can be recommended as a general approach to treating febrile seizures or as an approach to be used in groups identified to be at increased risk.

Keywords: Febrile seizures; Treatment; Prophylaxis

1. Historical perspective

Febrile seizures have been recognized for centuries. Thomas Willis, in his *Of Convulsive Diseases*, noted an association with teething but wisely stopped short of attributing teething as a direct cause (Fig. 1) [1]. Lennox, who cited Willis’ observation on teething, suggested that soothing words such as ‘benign’ and ‘simple’ did not present the whole picture with febrile seizures, and that it might be appropriate for clinicians to stratify cases for prognosis and treatment on the basis of such factors as focal features and clustering of seizures (Fig. 2).

The immediate treatment of febrile seizures is relatively uncontroversial. For example, there is general acceptance that prolonged febrile seizures should be treated using some form of status epilepticus protocol. It is advisable to check a blood glucose level, particularly if there is a long period of postictal obtundation. And most pediatricians agree that it is essential to rule out CNS infections in the form of meningitis or encephalitis, particularly in younger cases where the signs can be more subtle.

The more controversial questions relate to the value of treatments aimed at stopping or reducing the number of recurrent febrile seizures. This can be regarded as an end in itself, since febrile seizures are distressing and frightening for families and carers, but there is also the question of whether recurrent febrile seizures are on a causal pathway that leads to increased risks of later epilepsy. This review evaluates the rationale for secondary prophylaxis of febrile seizures, the potential effectiveness
of such treatment, and whether it can be recommended as a general approach to treating febrile seizures or as an approach to be used in groups identified to be at increased risk. It emphasises a few key influential papers, predominantly randomised-controlled trials, rather than providing a detailed overview. It discusses several treatment guidelines and more detailed reviews. And it suggests potential future directions for treatment strategies.

2. Antipyretic drug treatment

Randomised-controlled trials have shown that giving antipyretics with fever, either sporadically or regularly, does not reduce the risk of recurrent febrile seizures. This seems to be true of acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin [2]. Schnaiderman et al. showed that administration of paracetamol after an incident febrile seizure had no effect upon the risk of a subsequent febrile seizure within 24 h (paracetamol group 4/53 (8%) versus control group 4/51 (8%)) [3]. A similar lack of effect was described by Uhari et al., with or without the co-administration of rectal or oral diazepam [4].

One study of 70 children reported greater efficacy in terms of temperature reduction with ibuprofen than with paracetamol, with a mean difference between the two treatment groups of 0.5 °C 4 h after treatment [5]. A study of 230 children aged between 1 and 4 years randomly allocated treatments with ibuprofen (5 mg/kg every 6 h) or placebo during periods with rectal temperature above 38.5 °C [6]. With a median follow-up of 1 year, there were 67/230 (29%) recurrences of febrile seizure but no significant differences between the two treatment groups, both before and after adjustment for non-adherence to the treatment protocol.

Although they do not reduce the risk of recurrent febrile seizures, antipyretics are generally considered to make the child feel more comfortable and are usually administered for that purpose. They are widely administered, but there are small relative risks of hepatotoxicity (with acetaminophen) and metabolic acidosis, renal or respiratory failure, and coma (with ibuprofen) in overdose or where recipients have other risk factors [7–9]. One potential complication relating to future studies in this area is that benzodiazepine-receptor full agonists such as diazepam and lorazepam have been shown in animal models to have some antipyretic effect [10,11]. Any such effects in humans have yet to be elucidated, but one study has suggested no additive effect of diazepam co-administered with paracetamol [12].

3. Regular secondary prophylaxis with antiepileptic drugs

Several studies have shown that regular secondary prophylaxis with phenobarbital reduces the risk of further febrile seizures. A Canadian randomized double-blind study of 79 children compared the effects of giving a single daily dose of either phenobarbital or placebo as secondary prophylaxis of simple febrile seizures, with follow-up occurring over a 12-month period [2]. Compliance was monitored using a fluorescent tracer linked to riboflavin that was combined with the phenobarbital and placebo. Recurrent seizures occurred in 2/39 (5%) in the phenobarbital group compared with 10/40 (25%) in the placebo group (two-sided Fisher exact test, \( P = 0.025 \)).

A study in Manchester, UK enrolled 186 children aged between 6 and 72 months with a febrile seizure in the first year of life, a complex febrile seizure, or more than one febrile seizure in a 2-year period [13]. They were randomly allocated treatment in three groups: (1) rectal diazepam as rescue treatment of any subsequent prolonged febrile seizure (a form of control group); and regular prophylactic treatment with (2) sodium valproate or (3) phenobarbital. Overall, the risk of recurrence was 30%, and was not significantly lower in those allocated regular prophylactic AED treatment.
Ngwane and Bower studied 64 children with febrile seizures and randomly allocated them to receive regular sodium valproate or phenobarbital. Twenty-one children were reported as a control group, but they were not formally enrolled in the study or randomly allocated their control status. After 12 months’ follow-up, the reported recurrence of febrile seizures in those on valproate was 1/18 (6%); for those on phenobarbital, 4/21 (19%); and in the untreated group, 7/21 (33%). They reported a significant difference between valproate and untreated groups. This was not an intention-to-treat analysis, and two cases in each of the valproate and phenobarbital treatment groups were withdrawn because of side effects and not included in the analysis of febrile seizure recurrence. It is not clear whether or not those cases had recurrent seizures [14].

There have been relatively few studies of carbamazepine. One study showed no beneficial effect of carbamazepine in cases that had recurrent seizures on phenobarbital treatment [15]. A double-blind trial in 40 children compared carbamazepine against phenobarbital as secondary prophylaxis of simple or complex recurrent febrile seizures [16]. Recurrent febrile seizures were reported in 9/19 (47%) children allocated carbamazepine (with documented therapeutic blood levels) compared with 2/21 (10%) in the group treated with phenobarbital (2-sided Fisher exact test, \( P = 0.012 \)). The authors concluded that these results confirmed previous findings suggesting that carbamazepine is less effective than phenobarbital as a secondary prophylactic treatment of febrile convulsions.

Phenytoin also appears to have no significant treatment effect. A study of 138 children who had a first febrile seizure before the age of 2 years investigated the effects of regular secondary prophylaxis with phenobarbital (\( n = 48 \)), phenytoin (\( n = 47 \)), or placebo (\( n = 43 \)) [17]. Monitoring of blood levels showed that phenytoin concentrations were poorly controlled and often outside the ideal therapeutic range. Overall, phenytoin did not significantly reduce the incidence of further febrile seizures. The authors concluded that it is not an effective agent for prophylaxis of these seizures, noting that many of the recurrent seizures occurred in the context of subtherapeutic phenytoin blood concentrations. Phenobarbital was associated with a reduced risk of recurrent febrile seizures, but this effect seemed to be limited to cases where prophylaxis was started before the age of 14 months.

### 3.1. Adverse effects of treatment

Herranz and colleagues studied 95 children with febrile seizures that were assessed as being complex febrile seizures or having other risk factors for high incidence of recurrence [18]. Comparing the effects of regular secondary prophylaxis with phenobarbital, primidone, or sodium valproate, they reported side effects in three-fourths of those allocated phenobarbital and over half of those allocated primidone, with no significant differences in average phenobarbital blood concentrations between these two treatments (16.4 ± 2.8 mg/ml vs 14.1 ± 3.7 mg/ml) (primidone being a pro-drug of phenobarbital). Sodium valproate was associated with a lower proportion reporting side effects (45%) than phenobarbital. In the Manchester study, adverse effects were reported less often with valproate (24%) than with phenobarbital (61%), but the authors concluded that the benefit-risk ratio was insufficient to recommend either of these AEDs as secondary prophylaxis [19].

Reported adverse effects of phenobarbital treatment include effects upon mood, behavior and cognition, as well as somatic effects such as hypersensitivity reactions. Behavioral effects have been reported in over one-third of cases in some studies, with high incidences of hyperactivity, irritability, lethargy, and sleep disturbance [7,16,20–25]. One particular concern with long-term phenobarbital is the high incidence of depression [21,26,27]. Other studies have reported problems with phenobarbital to include impairment of short-term memory, and impaired attention and concentration [28,29].

One study of 217 children with febrile seizures at ages between 8 and 36 months were randomly allocated treatment with phenobarbital or placebo [20]. After 2 years of treatment, the reported mean IQ in the treatment group was 7 points lower (95% CI −2.5 to −11.5 points; \( P < 0.01 \)). Six months later, after treatment had been discontinued, the mean IQ in the phenobarbital group was 5.2 points lower (95% CI +0.04 to −10.5; \( P = 0.052 \)), a difference of borderline statistical significance but which might have been subject to a dilutional bias caused by non-compliance and a crossover rate of 30% to treatment from the placebo group. The authors concluded that phenobarbital impaired cognitive performance in children treated for febrile seizures and that this effect may outlast the administration of the drug by several months. Another study investigated interval changes in IQ between 6 months post-treatment initiation and 9 to 12 months later in children treated with phenobarbital (\( n = 32 \)) or valproic acid (\( n = 32 \)), comparing these with controls (\( n = 60 \)) who did not have epilepsy [30]. This study had the disadvantage of not examining pre-treatment baseline IQ, but showed that improvement in IQ on phenobarbital was poorer than in the valproate-treated and control groups.

In contrast, Camfield and colleagues found that children with febrile seizures who received regular treatment with phenobarbital for a period of 12 months did not have significant differences in IQ (assessed by Binet and Bayley Scales) compared with untreated controls [25]. Phenobarbital was assessed to disturb sleep and to increase ‘fussy’ behavior. In addition to behavioral problems, analyses suggested that there were some cog-
nitive problems. For example, there were reported problems with verbal language processing that were thought to be associated with the duration of treatment. And there were reported memory deficits that were reported to be associated with blood levels of phenobarbital. These adverse effects were reported to be more tolerable after 12 months of treatment than earlier.

4. Intermittent secondary prophylaxis with antiepileptic drugs

Adverse effects of regularly administered phenobarbital might be overcome by intermittent administration at times of fever. However, this has been shown to be ineffective. A Californian study showed that four-fifths of recurrent febrile seizures occurred within 24 h of the identified fever. Phenobarbital administered orally at the time of fever was no more effective than no treatment at all, in contrast with the reduction reported with regularly administered phenobarbital [31]. This lack of effect is probably due to the long half-life of phenobarbital and consequent long lead-time to effective blood and brain concentrations. Even though its half-life is shorter, valproate is similarly disadvantaged when administered orally in response to fever. A Danish study of 169 children compared valproic acid suppositories with rectal diazepam solution given in response to temperatures above 38.5°C [32]. By intention-to-treat analysis at 12 months, there were no significant differences in proportions with recurrent febrile seizures 16/80 (20%) versus 24/89 (27%) (Pearson $\chi^2$ 1.13, $P = 0.29$). A significantly lower proportion had reported side effects with valproate (37/80 (46%) versus 69/89 (78%), $\chi^2$ 17.6, $P < 0.001$). However, there were more recurrent febrile seizures classified as complex in the valproate group, and only a very small proportion in both groups had received treatments according to protocol.

Knudsen and colleagues studied 195 children with first febrile seizures occurring between 6 and 30 months of age, investigating the relative effects of intermittent or regular secondary prophylaxis [23]. One group was allocated rectal diazepam (5 mg suppository every 8 h) in response to a rectal temperature above 38.5°C, and the other group was allocated oral phenobarbital (2.5 to 4.5 mg/kg/day). A full intention-to-treat analysis was not performed. Thirty-nine children did not complete the study, and analysis was performed on the remaining 156 children (83 allocated diazepam and 73 allocated phenobarbital treatment). Febrile seizure recurrence rates were similar in both groups: 11% and 9% in diazepam and phenobarbital groups, respectively, at 6 months, and between 15% and 16% in each group at 12 months. There were no significant differences in seizure severity or duration. The authors concluded that regular long-term prophylaxis with phenobarbital had no benefits over intermittent treatment with rectal diazepam.

Intermittent secondary prophylaxis with benzodiazepines has been more extensively investigated. Rosman and colleagues reported a randomized, double-blind, placebo-controlled trial in 406 children with one or more febrile seizures and mean age of 24 months [33]. Oral diazepam (0.33 mg/kg every 8 h) was administered in response to any further febrile illness. With a mean follow-up of just under 2 years, they estimated a 44% reduction in relative risk for further recurrent febrile seizures (RR 0.56, 95% CI 0.38 to 0.81; $P = 0.002$). Almost 40% of the 153 children who received diazepam had reported side effects of moderate seriousness, such as ataxia, irritability and lethargy; but none were reported to have severe side effects, and these effects tended to settle with dose reduction. The authors concluded that oral diazepam given as intermittent secondary prophylaxis was effective and safe.

An eight-centre French study found less impressive results with an oral diazepam regimen of 0.5 mg/kg followed by 0.2 mg/kg every 12 h [34]. This randomised, placebo-controlled, double-blind trial enrolled 185 children aged between 8 months and 3 years with a first febrile seizure and normal neurologic development. Treatment was given in response to any rectal temperature above 38°C. One thousand days of prophylactic treatment resulted from 462 episodes of fever. After 12 months, there was no significant difference in the proportions progressing to a further febrile seizure (diazepam group 16% versus placebo 19.5%) but adherence to the treatment protocol was found to be poor. Only 1/15 children with recurrent febrile seizures in the diazepam group received treatment according to the trial protocol, and 7/18 children in the placebo group. In seven cases in each group, the seizure occurred before any fever was identified by the parents or carers, providing a further example of how challenging it is for families and carers to effectively implement a strategy of secondary prophylaxis.

Another Danish study investigated the effectiveness of short-term diazepam prophylaxis in febrile convulsions in a prospective, controlled study of 289 children who were enrolled after their first febrile seizure [35,36]. Rectal diazepam was allocated to 137 children with instructions that it be administered in response to any body temperature above 38.5°C, and 152 children did not receive diazepam in response to fever but were permitted to receive diazepam as rescue medication in the event of seizure recurrence. The active treatment group received a mean number of five doses of rectal diazepam per year. The proportions with recurrent seizures after 18 months were 12% versus 39% in treatment and control groups, respectively. Within 2 years, 3% of children in both treatment groups had developed non-febrile epileptic seizures. None of these cases developed
from the 230 children with simple febrile seizures. Risk factors for later epilepsy were initial complex febrile seizures and being assessed as having severe interictal EEG abnormalities.

4.1. Safety of intermittent benzodiazepine administration

The incidence of significant respiratory depression associated with benzodiazepine administration in the

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<td>above, upon risk of febrile seizure occurring within 24 h [3]. No effect (with</td>
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<td>or without rectal diazepam co-administration) when given in response to</td>
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<td>fever of 38.5 °C or higher [4]</td>
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<td>Ibuprofen</td>
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<td>recurrence risk similar to intermittent prophylactic rectal diazepam (9% vs</td>
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<td>11% at 6 months) [23]. No significant reduced risk of FS; 61% incidence of</td>
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<td>reported side effects, 20% of which led to early treatment withdrawal [13].</td>
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<td>14 months [17]. Side effects reported in 77% of cases [18]. Treatment</td>
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<td>discontinued in 32% because of side effects [31].</td>
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<td>Sodium valproate (or valproic acid)</td>
<td>Small study with effect estimate for recurrence of 6% (vs 19%) for</td>
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<td>risk of FS; side effects reported in 24%, with 6% having treatment</td>
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<td>withdrawn [13]. Side effects reported in 45% [18].</td>
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<td>Carbamazepine</td>
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<td>occurred on regular phenobarbital prophylaxis [15]. Significantly higher</td>
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<td>incidence of FS recurrence (47% vs 10%) when given as initial secondary</td>
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<td>Intermittent AED secondary prophylaxis</td>
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<td>as regular oral phenobarbital (11% vs 9% at 6 months; both groups 15–16% at</td>
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<td>12 months) [23]. Given orally as 0.33 mg/kg every 8 h in response to fever,</td>
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<td>FS recurrence relative risk reduced by 44% (RR 0.56; 95% CI 0.38 to 0.81);</td>
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<td>moderate side effects in 40% [33]. Oral regimen of 0.5 mg/kg followed by</td>
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<td>5 mg (7.5 mg if age over 3 years) every 12 h until temperature below</td>
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<td>38.5 °C; FS recurrence at 18 months significantly lower than control (12% vs</td>
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<td>39%) [35]. Risk of respiratory depression suggested to be low from registry</td>
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<td>Clobazam</td>
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<td>enrolled cases, as unit of statistical analysis (prone to trial-inflation and</td>
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<td>probably contributed to poor treatment adherence [43]</td>
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<td>Phenobarbital</td>
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<td>Given rectally, not significantly more effective than rectal diazepam (20% vs</td>
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<td>27%); significantly fewer side effects than rectal diazepam (46% vs 78%) [32]</td>
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context of febrile seizures is likely to be low. Knudsen reported that there were only two reports of diazepam-induced respiratory problems in Denmark between 1975 and 2000, a very low number considering that over two decades more than 30,000 have been exposed to rectal diazepam in Denmark alone [37]. This finding is congruent with other studies of diazepam safety, though not specifically in the context of febrile seizures [38–42].

The use of benzodiazepines other than diazepam is more restricted by the high incidence of side effects. Nitrazepam, for example, has been studied as secondary prophylaxis of febrile seizures with high reported rates of drowsiness, agitation and ataxia [43]. Brazilian and Indian studies of clonazepam reported relatively high incidences of side effects that included ataxia, hyperactivity, somnolence and recurrent vomiting [44,45]. The magnitude of treatment effects in these studies is difficult to compare with other studies because they used the number of later febrile episodes as the denominator for the reported treatment effect, rather than the number of enrolled cases with one or more subsequent febrile seizure.

5. Physician preferences and treatment guidelines

5.1. Descriptive studies of physician preferences

In the mid-1980s, a broad survey of management of febrile seizures was mailed to 10,000 child neurologists, neurologists, pediatricians, and family and general practitioners, with an overall response rate of approximately 50%. One-third or less of physicians prescribed anticonvulsive therapy only at the time of febrile illness, although this practice was much less common among recent graduates. Most cases with prolonged or focal seizures were prescribed regular AEDs or referred to a pediatric neurologist for further assessment [46].

In the early 1990s, Millichap performed a survey of pediatricians in Illinois and found that over half of the respondents reported using EEGs to inform the decision whether to give regular phenobarbital prophylaxis, with 90% of respondents stating that they would treat a complex febrile seizure with phenobarbital given as regular prophylaxis [47]. The reported mean duration of such treatment was 2 years. A broader questionnaire survey of members of the Child Neurology Society in North America showed that the preferred treatments for prolonged febrile seizures were intravenous phenobarbital, lorazepam and diazepam [48]. Long-term phenobarbital was prescribed by 89% for prevention of complex febrile seizures and by 43% for simple febrile seizures, with two-thirds of respondents stating that these choices were modified by the degree of perceived parental anxiety.

A survey published in 1998 reported the practice of 500 doctors in 14 Mediterranean countries [49]. It reported that antiepileptic drugs were generally not prescribed as regular secondary prophylaxis of febrile seizures, though this practice was common in Turkey and with a minority of doctor in France, Syria and Tunisia. A large number of doctors prescribed intermittent prophylaxis with a benzodiazepine.

These surveys are relatively old and it is likely that regular secondary prophylaxis of febrile seizures, including complex febrile seizures, is now administered much less commonly. However, it is also likely that there are substantial international and regional variations in practice. Guidelines have been published, though many of the recommendations pertain to simple febrile seizures rather than addressing the more challenging question of managing complex febrile seizures.

5.2. Guidelines

Guidelines relating to the neurodiagnostic evaluation of a child with a first simple febrile seizure have been published by the American Academy of Pediatrics Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures [50]. The guidelines recommend that lumbar puncture should be considered in any case presenting under the age of 18 months, and that it be strongly considered in children with the first simple febrile seizure presenting before the age of 12 months. On the basis of consensus and evidence, it recommended that EEG is not routinely performed in a neurologically well child with a first simple febrile seizure. It recommended that serum electrolytes, calcium, phosphorus, magnesium, complete blood count, and blood glucose not be routinely performed, but that blood glucose should be measured if there is a period of prolonged obtundation postictally. However, this recommendation does not preclude testing for the source of fever. It recommended that routine neuroimaging not be performed.

A clinical practice guideline relating to the long-term treatment of children with simple febrile seizures was published by the AAP in 1999 and has just been updated with similar conclusions (Box 1) [7,51]. These reports focus specifically on simple febrile seizures, which accounts for approximately 90% of incident first febrile seizures [52]. The technical report associated with the 1999 recommendation has a comprehensive review of evidence to that date [53].

Regular secondary prophylaxis with phenobarbital or valproic acid (or sodium valproate) was regarded as effective in reducing the risk of recurrent febrile seizures, but the benefit-risk ratio for these medications was regarded as insufficient to justify recommending such treatment. No medication has been shown to reduce the risk of later epilepsy. The use of intermittent secondary prophylaxis with diazepam was considered likely to reduce the risk of further febrile seizures, but was con-
sidered to have a relatively high risk of side effects and by families to have relatively low benefits. Antipyretic therapy was considered to have some benefits, but did not reduce the risks of further simple febrile seizures. In effect, the recommendation was that long-term treatment of simple febrile seizures is unjustified [54].

Recommendations from Japan were published in 1996 [55]. These suggested that most cases of febrile seizures can be followed with a laissez-faire approach, with consideration of treatment with intermittent diazepam, or regular phenobarbital or sodium valproate, being given in selected cases considered at higher risk. The authors identified the following risk factors, though explained that they thought the connotations of the term ‘risk’ to be rather too strong in this context where recurrence of febrile seizures does not necessarily lead to longer-term harm. The suggested factors relating to recurrence were: (1) febrile seizures starting before 6 months of age; and (2) history of febrile seizures in one or both parents. Warning factors for progression to epilepsy were: (1) neurological symptoms or signs, or developmental delay, before the onset of febrile seizures; (2) focal, prolonged, or clustered seizures; and (3) a history of epilepsy in first-degree relatives.

6. Potential future directions

Febrile seizures are common and subsequent serious adverse outcomes are rare. When there are serious outcomes, such as the later development of epilepsy, it is doubtful whether earlier treatment interventions, such as the secondary prophylactic antiepileptic treatments reviewed here, significantly modify the risks of such outcomes. However, there remains doubt and future studies are required to answer these questions effectively. In particular, the risks of febrile seizure recurrence are increased by such factors as earlier age at first febrile seizure, the first febrile seizure having features that make it ‘complex’ in nature, and a family history of epilepsy or of febrile seizures in a first-degree relative. Knudsen found that these factors, along with a history of day care nursery attendance, increased the risks of recurrent febrile seizures substantially, with 18-monthly recurrence rates of between 80 and 100% if there were three to five risk factors in the individual; 50% if there were two risk factors; 25% where there was only one factor; and 12% if there were none [36]. If such risk factors are reliable, future study designs might reserve secondary prophylaxis for cases with higher risks of seizure recurrence, possibly modifying risks of later epilepsy that have been undetected in studies with greater dilutional bias.

The associations between febrile status epilepticus, acute hippocampal injury, mesial temporal sclerosis, and later temporal lobe epilepsy remain controversial [56]. Future studies will help to elucidate these relationships and might suggest effective strategies for preventing progression to epilepsy. However, there are many challenges. For example, results from the North American multicenter prospective FEBSTAT study show that most cases of febrile status epilepticus occur as the first febrile seizure episode [57].

Another potential future development is screening for genetic risk factors such as channelopathies. Combining knowledge of such genetic predisposition – with or without an associated family history of febrile seizures or epilepsy – with other risk factors might lead to further targeting of cases and increases in the benefit-to-cost ratio for prophylactic treatment interventions. Potential interventions might relate to immunizations or reduction of exposures to viruses that might modify risks of longer-term epilepsy. Human herpesvirus 6 (HHV6), for example, is known to be associated with febrile seizures and might be a target for immunization or other interventions [58]. The interleukin-1 system has been shown, in animal models, to have an effect that might be unrelated to the endogenous pyrogen effect of these proteins, and it has been shown that the ratio of IL-1β to IL-1 receptor antagonists has an effect upon hippocampal neuronal excitability [59]. At present, it appears that few of these factors are likely to lead to innovative treatment interventions, but a combination of basic science and epidemiologic knowledge might lead to a significant breakthrough that does reduce the risk of progression to later epilepsy.
7. Summary and conclusions

The case for secondary prophylaxis of febrile seizures is controversial and not compelling [37]. In most cases, febrile seizures are benign, with low risks for progression to epilepsy and no convincing evidence that secondarily preventing recurrent febrile seizures modifies any such risk. However, they are very distressing to families and carers, and the overall recurrence rate is high, at around one-third for an incident case of first febrile seizure. Secondary prophylaxis is generally inappropriate in the case of simple febrile seizures, but for complex febrile seizures, and especially cases in which there are prolonged febrile seizures with focal features, secondary prophylaxis is considered more seriously because of the increased risks of later epilepsy (Table 1).

Antiepileptic treatments are not proven to reduce the recurrence risk for febrile seizures, but they do help control fever and will usually make the child more comfortable during febrile illnesses.

In most cases there is no indication for regular prophylaxis with antiepileptic drugs. Phenytoin and carbamazepine have been found to have no benefit as secondary prophylaxis. There is good evidence that phenobarbital reduces the incidence of subsequent febrile seizures when given as regular secondary prophylaxis, and some evidence from smaller studies that valproate is also effective. However, it is generally felt that their side effects outweigh likely benefits. There is no evidence that phenobarbital or valproate reduce the risk subsequent non-febrile seizures, or of the longer-term outcome of epilepsy.

Intermittent, rather than regular, prophylaxis with phenobarbital or valproate is not proven to be effective at reducing the incidence of subsequent febrile seizures. Intermittent use of oral or rectal diazepam, and potentially of other benzodiazepines, is an option that can be offered to families where there is very high anxiety about further febrile seizures, although studies have not consistently reported benefits. This approach is not likely to lead to significant harm or longer-term problems with behavior or cognition, but there is a relatively high incidence of clinically significant short-term side effects that is likely to lead to poor adherence with such interventions. Also, the strategy is often undermined by the tendency for febrile seizures to recur before the fever is identified. For families where there are high anxiety levels about further febrile seizures, however, intermittent secondary prophylaxis can be offered as a practical therapeutic option.

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