

An exploration of factors influencing the management of febrile seizures and effectiveness of conventional antipyretics at prevention of recurrence – a literature review

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Abstract

Background 2-5% of children will have a febrile seizure before the age of five. Most are categorised as simple but they can be complex and carry the risk of complications. They can be frightening for parents. Current UK guidelines advise against the use of antipyretic drugs for the prevention of recurrent febrile seizures but to also be mindful of parental sensitivities.

Aim This systematized literature review aimed to appraise the current global body of evidence in relation to current guidelines on using conventional antipyretics for the prevention of febrile seizures and explore factors which influence the management of febrile seizures.

Methods A research question was developed using the PICO framework and two databases were searched to find relevant primary research. Abstracts were screened to ensure relevance to the research question.

Findings Thirty-four articles were identified, nineteen abstracts were screened and three were found to be relevant to the research aim. These were critically appraised using the Mixed Methods Appraisal Tool and five themes were identified.

Conclusion One study found that paracetamol may prevent recurrent febrile seizures, one study found a small reduction in febrile seizure recurrence when treated with an antipyretic and one study found antipyretics ineffective at reducing febrile seizure recurrence. Similar, contemporary studies conducted on the current UK population may help to improve understanding of the factors influencing febrile seizure management and the effectiveness of antipyretics.

Keywords Febrile, seizures, convulsions, antipyretics, paracetamol, ibuprofen

Key points

- This systematized literature review demonstrates that there is no consensus on the effectiveness of conventional antipyretics in the prevention of febrile seizures.
- Clinicians have an important role in educating parents and caregivers about fever and febrile seizures.
- A range of definitions of fever may be in use.
- First febrile seizures are most likely to occur between the ages of six months and five years but subsequent febrile seizures may occasionally occur after this age.

Reflective questions

- Would you administer an antipyretic to a child who had had a febrile seizure?
- What factors influence your decision making when considering whether to give an antipyretic when attending a patient presenting with a febrile seizure?
- What information do you think it is important to discuss with parents/caregivers of a child who has had a febrile seizure?

Introduction

Fever is a common childhood complaint with 20-40% of parents and carers reporting an episode each year (National Institute of Health & Care Excellence (NICE), 2019). The most common cause of fever is infection (El-Radhi, 2009). Febrile seizures (FS) occur in 2-5% of healthy preschool children and recur in approximately 40% of these patients (Whelan et al., 2017; National Institute of Neurological Disorders & Stroke, 2021). Using Whelan et al.'s (2017) statistics it can be extrapolated that 76,000-190,000 children may experience a FS in their first five years. Children who have complex FS - defined as such if they last longer than

15 minutes, recur within 24 hours or have associated focal neurology - may have an increased likelihood of mortality in the subsequent two years and are 3.6-5.6% more likely to develop epilepsy, a cause of mortality for 40-80 children per year (Smith et al., 2019; Royal College of Paediatrics & Child Health, 2013). NHS advice for a first FS is to call 999 or attend an Emergency Department so it is considered likely that ambulance crews attend FS with some frequency (Ahmed El-Esrigy, 2021; NHS, 2019). As acknowledged by Daneman & MacArthur in 1978, children who present with FS may have been given anticonvulsants but this treatment started to change at around this time.

Thermoregulation maintains the body at an optimal temperature for normal cellular function but can be disrupted by infection and resultant fever (Osilla et al., 2021). The innate immune response stimulates the secretion of pro-inflammatory cytokines and prostaglandins which act on thermosensitive neurons in the hypothalamus to effectively raise the thermostat of the hypothalamus (Osilla et al., 2021). These cytokines may also directly affect neuronal excitability at a stage in a child's development where neurons may be in an enhanced excitatory state (Jensen et al., 2002, cited in El-Radhi, 2009). This may lower the threshold for seizure activity.

UK ambulance services use clinical practice guidelines produced by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) which currently advises against antipyretics for FS but also that parental sensitivities should be considered in relation to fever (JRCALC, 2019). These are supported by National Institute for Health and Care Excellence (NICE) guidelines Fever in Under 5s: Assessment and Management (2019). This systematized literature review will analyse the body of evidence linked to the use of paracetamol and ibuprofen versus placebo or no antipyretic medication and explore factors influencing the management of febrile seizures.

Method

A systematized literature review was chosen to critically appraise, consolidate and summarise the existing evidence base. First described by Grant & Booth (2009), a systematized review includes some of the elements of a systematic review but does not meet

the methodological requirements of a systematic review and does not usually include exhaustive searching. They are often conducted by a single reviewer.

The question that this review intends to answer is whether conventional antipyretics are effective in preventing the recurrence of febrile seizures. The PICO framework was used to develop the question. This is illustrated in Table 1 below.

Table 1. PICO Question

	Framework element	Titular question element
P	Participant(s)	Children with FS
I	Intervention(s)	Oral paracetamol or ibuprofen
C	Comparison/control	No antipyretic medication
O	Outcome	Recurrence of FS

A search of the literature was conducted over two databases – Medline and CINAHL. Medline is widely renowned for its high concentration of healthcare literature and benefits from Medical Subject Headings controlled vocabulary increasing the likelihood of relevant results (National Library of Medicine, 2021). CINAHL is also healthcare focused and gives access to in excess of 1300 academic journals worldwide (Ebsco, 2023.). The primary outcome measured was whether a febrile seizure recurred.

The search terms used were FS and the alternative febrile convulsion, antipyretic and its alternative spelling anti-pyretic, ibuprofen, paracetamol and acetaminophen. Wildcard searches were used to search for plurals of the terms seizure, convulsion, antipyretic and anti-pyretic in order to include results with these terms. Combinations of the search terms were used with the Boolean operator AND to return results which included both terms. The inclusion and exclusion criteria are summarised in Table 2.

Inclusion	Exclusion	Rationale
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Children aged 6 and younger	Children aged 7 and older	This is the age at which FS are prevalent
Publication year 2000-2021	Publication pre-2000	Studies are more recent and therefore perhaps more generalisable.
Worldwide publications in English language	Language other than English	Reviewer is English speaking only.
Published in an academic journal	Not published in an academic journal or grey literature	Studies meet the standards required of academic journals and should therefore be ethically sound.

Table 2. Inclusion and exclusion criteria

Snowball sampling was considered and reference lists were appraised but no studies met the inclusion and exclusion criteria. One author (VLD) was responsible for assessing whether studies met the inclusion and exclusion criteria.

Results

The literature search was conducted in November 2021 and 34 articles were identified. Sixteen were excluded once inclusion and exclusion limiters were applied and three articles were found to be suitable for inclusion in this review. Duplicate results were automatically excluded by the database search facility. The process is illustrated in Figure 1.

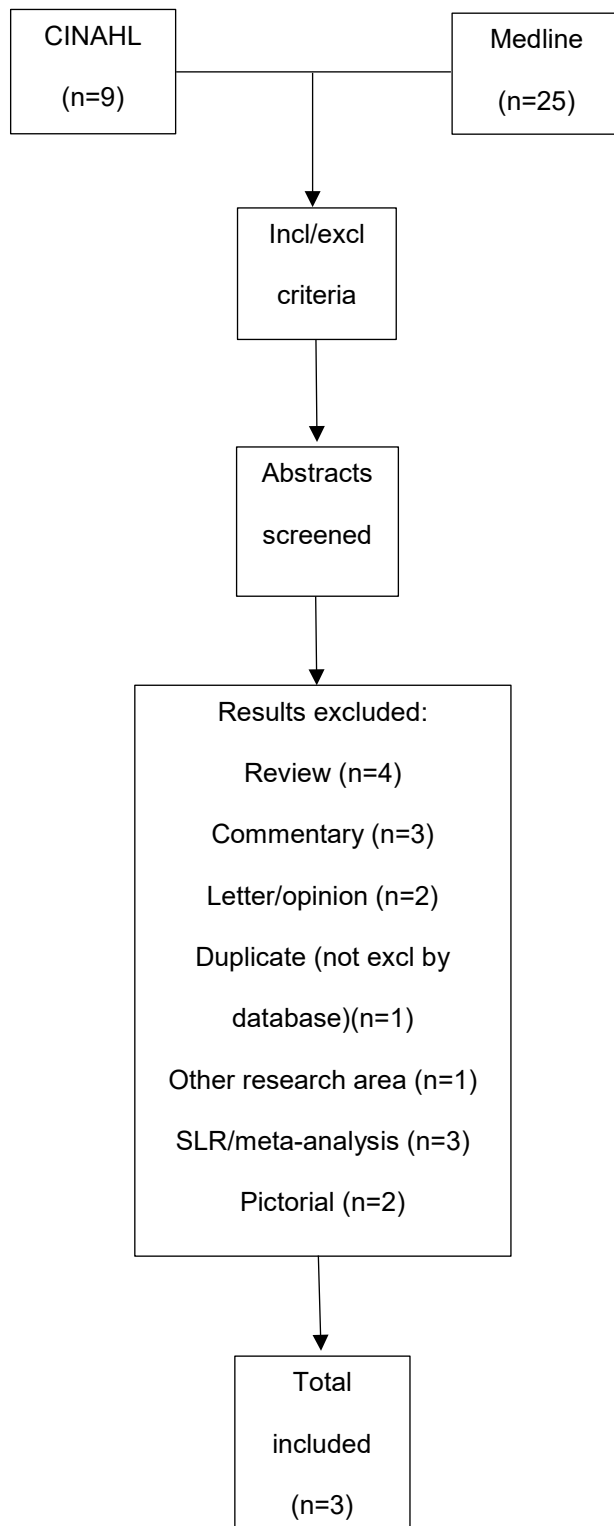


Figure 1. Results of literature review and selection process.

Table 3 details the included studies and summarises each study's outcomes.

Study/Authors/Year	Objective	Design	Country	Sample size	Interventions	Outcomes
A study of the efficacy of antipyretic drugs in the prevention of febrile seizure recurrence. Van Esch et al. 2000	To compare the efficacy of ibuprofen versus paracetamol at antipyresis in children with FS when compared with children given no antipyresis.	Combined experimental and descriptive patient series	Netherlands	212	Paracetamol versus ibuprofen versus no intervention.	A 5.4% reduction in FS recurrence in groups treated with an antipyretic compared to no antipyretic. Confidence interval 95% (range 0.2-1.2). $P = 0.74$.
Antipyretic Agents for Preventing Recurrences of FS. Strengell et al. 2009	To compare the efficacy of antipyretics in preventing recurrent FS.	RCT	Finland	231	1: Diclofenac versus placebo; then 2: Ibuprofen versus paracetamol versus placebo.	Antipyretics are ineffective at preventing FS and at antipyresis in fever episodes that led to FS. Confidence interval 95% (-12.8-17.6). $P = .99$.

Acetaminophen and FS Recurrence During the Same Fever Episode. Murata et al. 2018	To assess the efficacy of paracetamol in preventing recurrent FS.	RCT	Japan	423	Paracetamol versus no intervention.	Paracetamol may prevent recurrent FS in the same fever episode. Confidence interval 95% (2.3-13.3). <i>P</i> = <.001.
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Table 3. Studies Included and Summary of Outcomes

Two studies are randomised controlled trials (RCTs) and the third, Van Esch et al. (2000), compares the results of a previous randomised crossover trial (treatment vs treatment) with an observational study providing a control element. The hierarchy of evidence places RCTs above observational studies so RCTs can be held in higher regard (Wallace et al., 2022). Healthcare systems in Finland, Japan and Netherlands are similar to that of the UK, being either free or subsidised by government and affordable for most of the population so any results could be considered generalisable to the UK population.

Quality Review

All abstracts identified were reviewed by the primary author. A shortlist of abstracts was used to guide full-text reviews, and papers were included if they examined FS and antipyresis. All included studies were assessed for their methodological quality with the use of the Mixed Method Appraisal Tool (MMAT) developed by Hong et al. (2018). MMAT was chosen for its versatility and adaptability to various methodologies, while focusing on the fundamental principles of methodological quality assessment in empirical studies. In line with the guidance provided by the authors of the MMAT tool, both authors carried out thematic synthesis and concluded the assessment with the same scores.

Following the systematized search and appraisal of the studies five themes were identified. These are the effectiveness of antipyretics, the definition of fever, the site at which body temperature should be measured, the discrepancy in the age range of participants and parental fear of FS.

Discussion

Effectiveness of antipyretics

One aim of this systematized review was to assess the effectiveness of paracetamol or ibuprofen when compared with no intervention in the prevention of FS. The largest sample of all the included studies was used by Murata et al. (2018) which strengthens the validity of this study. Participants were only followed up for 24 hours after enrolment however, so it could

be considered that their results are most generalisable to this period only. Though Murata et al.'s (2018) results are statistically significant they contradict current JRCALC guidelines.

Van Esch et al. (2000) also analysed risk of FS recurrence by recording temperature prior to FS and first-degree relative history of FS. Their results are not statistically significant but suggest that antipyretics may be minimally beneficial to those participants with a higher risk profile. However, Van Esch et al. (2000) followed up the treatment group for a shorter period than the control group. This was corrected for in statistical analysis but this could still represent potential bias affecting the results. It is also concerning that participants that were non-compliant with treatment protocol were not excluded from analyses.

Strengell et al. (2009) was the only study to also investigate the effectiveness of diclofenac. Participants in this study were randomised to either diclofenac or placebo then again to either paracetamol, ibuprofen or placebo. The effect of diclofenac on paracetamol and ibuprofen is unclear, however, a more recent study by Sharif et al. (2016) found diclofenac to be more effective at antipyresis than paracetamol. The study design makes true synthesis of the results difficult as well as potentially affecting the study's reliability and validity. However, the study's use of placebo may positively affect the study's validity.

Murata et al. (2018) was the only study to analyse recurrence data stratified by age group. The study found paracetamol was more effective at preventing FS recurrence in the 22-60 month age group with a 4.1% recurrence rate compared with a 13.2% recurrence rate in the 6-21 month age group. Clinicians who decide to treat FS with an antipyretic could consider these findings and be aware that treatment might be more successful in those 22 months and older. However, no other supporting evidence could be found and this is not supported by JRCALC guidelines (2019).

Definition of fever

A limitation of the studies is the discrepancy between the definitions of fever used which makes the findings more difficult to compare and calls into question the validity of the studies.

The body temperature given as the starting point for interventions varies by 0.5°C between the studies which presents a question of whether findings would have been different if the same definition of fever had been used. However, multiple definitions of fever are used in the studies, as in practice.

The NICE Clinical Knowledge Summary (2018a) defines fever in children as ‘an elevation of body temperature above the normal variation’ though, for clarity, gives a figure of 38°C. The definition recognises that fever can be hard to define. Rather than focusing on body temperature as a diagnostic tool, the NICE guidelines for Fever in Under Fives (2019) direct clinicians to consider body temperature in the context of other signs and symptoms such as respiratory rate, heart rate and urine output. This is supported by the work of El-Radhi (2009) who writes that the appearance of a child is more important than body temperature alone.

A lack of consensus is apparent when searching literature though many authors refer to institutions such as the NHS, NICE, The American Academy of Pediatrics and Stanford University as using 38°C as the definition of fever (NHS, 2020; NICE, 2018a, Wallenstein et al., 2012). It is acknowledged that in all cases the study authors had to set a temperature to be the indicator for the commencement of intervention – failure to do so would likely have resulted in results with very low validity and reliability. However, evidence-based guidelines and wider policy seem to deemphasise having one figure as being considered the start of fever and encourage the view that body temperature is a spectrum affected by multiple factors and that fever as a standalone symptom is not something to be treated but to be considered in a wider context.

Site of body temperature measurement

Differences between the included studies were found regarding the site used for thermometry. Van Esch et al. (2000) specified that participants’ temperatures should be measured rectally but Murata et al. (2018) and Strengell et al. (2009) failed to specify a site which calls into question the internal validity of those studies. All included studies involved temperatures being monitored at home by participants’ parents and in the absence of specific instruction it is possible that parents would have chosen varying sites and may not have taken

temperatures as accurately as clinicians. These studies' results may have been impacted by these discrepancies as well as the fact that different sites are more or less reflective of true core temperature.

Rectal thermometry has long been considered the most accurate and reflective of true core temperature with oral temperatures lower on average and tympanic and axillary temperatures less accurate (Barbi et al., 2017). However, rectal thermometry is not recommended by current NICE guidelines (2019) as there is evidence to suggest that rectal temperatures are slow to change in response to a change in core temperature and are affected by the presence of stool (Canadian Paediatric Society, 2000). Moreover, different sites may have variable accuracy and practicality in different aged children. Rectal thermometry may be considered inappropriate for the emergency clinician who must consider patient dignity, distress and the speed at which thermometry can be obtained.

Age discrepancy

The studies approached age differently with Murata et al. (2018) using an institutional definition to set age ranges for participants. Strengell et al. (2009) refer to a textbook definition but then include children younger than this without explanation and Van Esch et al. (2000) do not give a rationale for the age range of participants. The youngest participants enrolled in any of the studies were four months though there is a general consensus among the wider evidence that FS occur from six months. For example, this is stated in British Medical Journal (BMJ) Best Practice (2019) and NICE (2018b) guidelines which are the basis for JRCALC guidelines used by ambulance services (JRCALC, 2019).

Van Esch et al. (2000) specify that participants must be older than 10 months but the reason for this is unclear. It was considered that this could be due to dose unsuitability for children younger than 10 months however the study protocol calls for participants to be given doses lower than those currently recommended by the British National Formulary for Children (BNFc) (BNFc, 2023a; BNFc, 2023b). This calls into question the study's internal validity; a higher dose may have produced different results.

The upper age limit for inclusions varied more widely between three to five years, excluding follow-up periods of two years in the studies by Strengell et al. (2009) and Van Esch et al. (2000). Vestergaard & Christensen (2008) conducted a large study over 28 years finding that 93% of first FS occurred by the age of four and all participants had their first FS by the age of five. In this study, no participants over the age of five were found to have had a first FS, however, this excludes participants having a second or subsequent FS after this age. Ogino et al. (2020) specifically studied late FS (i.e. occurring after age five) and found that 90% of participants had one FS after the age of five but 10% had more than one with a significant decrease in their occurrence after the age of nine. They also found that FS can occur as late as 14 years old. This may show that the included studies excluded some potential participants.

NICE (2018b) clearly state that FS occur between six months and five years whereas BMJ Best Practice (2019) states they are “most common” between six months and five years, acknowledging that they can occur at other ages. This reflects that FS later in childhood are rare but may also aim to ensure that seizures which occur after the age of five are subject to higher scrutiny regarding their aetiology. Emergency clinicians should consider the age, medical history and the history of the presentation when considering whether an FS has occurred and consider differential diagnoses which may require different treatments.

Parental fear

All included studies acknowledge that FS can be frightening for parents and carers who witness them and incorporate this reasoning into their study rationales.

Interviews conducted on a small sample by Westin & Levander (2017) regarding the parental experience of FS found that parents felt unsure of what was happening or anxious that the child could die. Anxiety during subsequent episodes of fever could persist for up to two years and some parents subsequently gave antipyretics in response to any fever episode. Millichap (1999), commenting on two studies, reports fear of FS and/or fever in almost 50% of parents

of children after an FS and found that those with lower levels of anxiety around fever and FS attributed this to information from healthcare professionals. This evidences the impact that healthcare-led parental education can have. Pre-hospital clinicians, who may be present early in the timeline of FS, can contribute greatly to parental education during and after the emergency and have an impact on how distressing parents find the situation.

There is evidence to suggest a wider issue of parental “fever phobia”. Purssell (2013) describes six studies that found parental anxiety around fever. The most recent, by Chiappini et al. (2012), found that all parents surveyed believed that fever itself could be harmful. This study and another by Sakai et al. (2012) found that parents consider healthcare professionals their primary source of information on fever, again evidencing the potential impact of healthcare-led parental education. Moreover, there are potential risks associated with fever phobia. These include giving higher than recommended doses of antipyretics, though this can be balanced with the advantage of increased vigilance (Purssell, 2008). Parental education could aim to inform parents of the risks of accidental overdose as well as the immunological role of fever. Research on the benefits of parental education has focused more on behavioural rather than clinical aspects but has been found to be effective (Morawska et al., 2015).

JRCALC (2019) guidelines advise that parental sensitivities should be considered when deciding whether to treat a fever with antipyretics. Shared decision-making was found to be essential for family-centred care based on respect and trust by Jordan et al. (2020) who also found little evidence for the perceived barriers to shared decision-making reported by healthcare professionals. The evidence demonstrates that a balance should be struck between allaying parental fear and concern by treating a fever or FS with medication and educating parents as to the benignness of fever and FS.

Limitations and future research

It is important to acknowledge that this review is not without limitations. One author conducted the searches which may have subjected the review to article selection bias, though this was limited by the use of homogenous search criteria used across the databases. The search did

not identify any studies conducted in the UK, however the healthcare systems of the countries where the included studies were conducted are similar in standard to that of the UK. Conducting searches of additional databases and literature not published online may have yielded a higher number of articles for consideration.

Similar, contemporary studies conducted on the current UK population may help to improve understanding of the factors influencing febrile seizure management and the effectiveness of antipyretics. Further research into parental education surrounding febrile seizures may be beneficial.

Conclusion

Two of the included studies found that antipyretics were ineffective or not significantly effective at preventing FS recurrence and the study with the largest sample found that FS *may* be effective at preventing the recurrence of FS. Therefore, the findings of this review are not unanimous.

The aims and objectives of this systematized review were met but consensus on best practice in the management of febrile seizures and the effectiveness of conventional antipyretics in the prevention of recurrence has not been reached therefore necessitating further research.

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