

# Who's afraid of fever?

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The nurses on the children's ward used to have a very fixed approach to fever in young children. If the child had a temperature of 38°C, they would strip the child down and ask the junior doctor on duty to write up some paracetamol. If the child had a temperature of 39°C, they would ask the doctor to write up ibuprofen as well as paracetamol. The doctors would readily comply with these requests.

These practices raise a number of questions. Why are we trying to reduce body temperature in a child with fever? Is fever dangerous in itself? Is a child with a high fever more likely to have a serious underlying cause? What are the benefits of trying to reduce a child's fever? Conversely, and given that fever is part of the body's natural response to infection, should we try to reduce a child's temperature at all? Are physical methods of cooling effective? Are antipyretic drugs effective, and, if so, which ones should we use? Are they safe? Are two agents better than one?

We (the authors) are two of the developers of the National Institute for Health and Care Excellence (NICE) evidence-based guidelines on feverish illness in young children.<sup>1 2</sup> As such we looked at all of the above questions in both the original 2007 guideline and its 2013 update. Systematic reviews were carried out on all of the most important questions. In this article, we will look at the answers we found to these questions. We will also look at more recent evidence.

## IS FEVER DANGEROUS IN ITSELF?

It is well known that fever is a cause of great concern for parents and carers. Fever is one of the three things that parents fear most when their children are acutely unwell.<sup>3</sup> (The other two are cough and the possibility of meningitis). Many parents believe that fever can cause brain damage, coma and death, as well as the more common fears of convulsions and dehydration.<sup>4-7</sup> A number of these fears,

including the risk of brain damage, are shared by some healthcare workers.<sup>7-9</sup>

It is true that very high body temperatures can disrupt cellular metabolism and cause organ damage. Temperatures above 41.5°C are sometimes seen in cases of hyperthermia, and temperatures this high can cause significant morbidity including brain damage.<sup>10</sup> However, hyperthermia is the result of an uncontrolled rise in body temperature. Fever, in contrast, is a regulated rise in body temperature. It is, in effect, a controlled resetting of the body's thermostat. As such, dangerously high temperatures are rarely, if ever, encountered in children with feverish illnesses. This 'glass ceiling' effect with fever was noted by DuBois as long ago as 1949.<sup>11</sup>

From the above, it is not surprising that we did not find any evidence from our searches to suggest that fever is dangerous in itself. Fear of fever almost certainly results from ignorance of the fact that any mortality or morbidity from feverish illness is caused by the underlying infection. Most healthcare professionals are aware of this point, of course, but we could do more to put the message across to parents and carers.

## IS A CHILD WITH A HIGH FEVER MORE LIKELY TO HAVE A SERIOUS UNDERLYING CAUSE?

We conducted a systematic review on the relationship between the height of fever and the incidence of serious illness for the original NICE guideline.<sup>1</sup> Nine prospective cohort studies were included in the review. Six of the studies reported that the incidence of serious illness increased with body temperature and three did not. In general, the studies that did report an association found the predictive value of a high temperature to be poor. Also, many children with a serious illness did not have a particularly high temperature. However, some of the studies looked at children of different ages and there did appear to be a higher predictive value of a body temperature >39°C in children under the age of 6 months, and even more so in infants under the age of 3 months.<sup>12</sup>

For the revised guideline, we identified six more studies that looked at the relationship between height of fever and serious illness. The findings in these were

very similar to those reported earlier, so we did not repeat a full systematic review. Notably, the new papers included the report of the Australian FEVER study.<sup>13</sup> This prospective cohort of nearly 16 000 febrile episodes is by far the largest study of feverish illness in children ever undertaken. The FEVER study confirms the trend towards a higher incidence of serious illness with increasing temperature but the predictive value remains limited.

In summary then, there is a trend towards a higher incidence of serious illness with increasing temperature, but this association is not strong and its predictive value is poor. The incidence of serious infection in previously healthy children has fallen dramatically in recent decades following the introduction of conjugated vaccines.<sup>14 15</sup> It is therefore likely that the predictive value of a high temperature will now be even lower.

## WHAT ARE THE BENEFITS OF TRYING TO REDUCE A CHILD'S FEVER?

From the above, it is clear that fever is not harmful. Why then would we want to reduce a fever? One reason is to treat the symptoms found with fever rather than fever itself. Children are often uncomfortable or distressed during feverish illnesses, and they may have poor feeding and disrupted sleep. Pain and swelling are well-known consequences of the inflammatory response, and, as such, they are often seen in childhood infections. The drugs commonly used to treat fever in children are also analgesics and one is also an anti-inflammatory agent. It may well be that the main benefit of antipyretic agents comes from these properties, and we would argue that symptoms such as pain and distress are very reasonable reasons to intervene.

Another reason that is often given for treating fever is to prevent convulsions, especially in children who have previously had febrile convulsions. We found one good quality review and one Cochrane review that addressed the issue in children with a history of febrile convulsions.<sup>16 17</sup> There were few high-quality studies, but both reviews concluded that there was no evidence that antipyretics prevent seizures. More recently, a good quality randomised controlled trial showed no difference in the incidence of further seizures with prophylactic antipyretic agents.<sup>18</sup> This study also showed that most febrile convulsions occur at the onset of fever, and this probably explains why prophylaxis does not work.

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## CONVERSELY, AND GIVEN THAT FEVER IS PART OF THE BODY'S NATURAL RESPONSE TO INFECTION, SHOULD WE TRY TO REDUCE A CHILD'S TEMPERATURE AT ALL?

Fever is part of the body's natural response to infection. It is therefore reasonable to assume that there must be some benefit to it. In evolutionary terms, the host's inflammatory response would not have been maintained through the generations if it did not produce an increased chance of survival. In more biological terms, there is evidence that some microorganisms are adversely affected by temperatures above 37°C and some host response mechanisms perform better at higher body temperatures.<sup>7</sup>

So, if fever is advantageous, is there any evidence that trying to prevent fever will result in a worse outcome? Our searches produced little good quality evidence to answer this question, but we did find some observational studies. One study reported that the regular use of paracetamol in children with chickenpox delays the healing of vesicles.<sup>19</sup> Another, in critically ill adult patients, reported that the use of antipyretics is associated with increased mortality.<sup>20</sup> In another study, it has been shown that the prophylactic use of paracetamol results in reduced antibody titres against childhood vaccines.<sup>21</sup> On the other hand, a recent systemic review of five randomised controlled trials has reported that the regular use of antipyretics is not associated with an increased duration of illness.<sup>22</sup>

The evidence base on the benefit of fever is still very limited, but we would suggest there is still a theoretical reason to allow fever to run its course. We should not treat fever automatically in children who are not distressed.

## ARE PHYSICAL METHODS OF COOLING EFFECTIVE?

Traditional physical methods of cooling include undressing, fanning and tepid sponging. We found no evidence for any benefit from undressing or fanning. Tepid sponging may produce a short-lived reduction in body temperature, but this is often accompanied by shivering and crying.<sup>17</sup> The use of tepid sponging is therefore counterproductive if we accept the premise that the main purpose of treatment is to alleviate suffering. Deliberately exposing febrile children to the cold is likely to be inappropriate for the same reason.

## ARE ANTIPYRETIC DRUGS EFFECTIVE, AND, IF SO, WHICH ONES SHOULD WE USE?

Paracetamol and ibuprofen are the two drugs that are most widely used for the treatment of fever. Our reviews confirmed that they are both highly effective in reducing body temperature in children with fever.<sup>1 2</sup> When compared with each other, most studies have found that ibuprofen produces a slightly larger reduction in body temperature than paracetamol. The effect of ibuprofen also appears to last longer. However, most of the studies used paracetamol at doses below those recommended in the UK. Moreover, the effect on body temperature was the only outcome reported in most studies. Data on the effect on fever-associated symptoms, such as discomfort, are sparse. We found only one study that compared the effect of paracetamol and ibuprofen against such symptoms.<sup>23</sup> There was no difference.

## ARE THEY SAFE?

The key issue in any medication is safety. The main problem in assessing the safety of antipyretic drugs is the lack of data. Although systematic reviews have been undertaken, these are reviews of studies that were generally underpowered or insufficiently sensitive to identify toxicity in many cases.<sup>24</sup> At the other end of the scale are case reports and series that suggest a range of toxicities. These include gastrointestinal bleeding, renal injury and secondary infections for ibuprofen; and liver toxicity and asthma for paracetamol.<sup>25-28</sup> In general, these side effects appear to be rare.

More of a concern is likely to be giving too much of these drugs, either because too large a volume is given or because they are given too often.<sup>29</sup> Errors in dosing are not restricted to parents either; data from Scotland suggesting that many prescriptions from general practitioners contain errors.<sup>30</sup>

## ARE TWO AGENTS BETTER THAN ONE?

As we have seen, healthcare workers and parents are sometimes tempted to treat feverish illnesses with two antipyretic agents instead of one. In practice, this can be done in two ways: combined treatment in which both drugs are given at the same time or alternating treatment in which the second drug is introduced at a later stage.

In our initial reviews, we found no evidence from a number of small randomised controlled trials that combined treatment with paracetamol and ibuprofen was more

effective at reducing body temperature than using either agent alone.<sup>1</sup> None of the trials looked at outcomes other than reduction in body temperature. The updated review included a larger study that did suggest that combined treatment resulted in a statistically significant reduction in duration of fever compared with paracetamol alone.<sup>2 23</sup> However, there was no difference versus ibuprofen alone so the apparent superiority of combined treatment is probably due to the longer duration of action of ibuprofen. Moreover, this study did look at outcomes such as discomfort and there was no benefit from using paracetamol and ibuprofen together. More recently, a meta-analysis was performed as part of a Cochrane review of combined antipyretic agents.<sup>31</sup> This demonstrated a statistically significant reduction in mean body temperature when using combined agents. However, the difference was very small (0.27°C at 1 h), so the finding is probably not of any clinical significance.

In contrast to combined treatment, there is some evidence that alternating antipyretics may be beneficial in certain situations. We found two randomised controlled trials that looked at introducing a second agent if there had not been an adequate response to the first agent.<sup>32 33</sup> Both of these studies reported a significant benefit in terms of temperature reduction compared with placebo. Moreover, one of the studies reported a significant reduction in discomfort and pain with the alternating regimen.<sup>33</sup>

## FROM EVIDENCE TO GUIDANCE

From the above discussions, it should be clear how the NICE Guideline Development Group came to their conclusions and recommendations about fever. The relevant recommendations from the 2013 guideline are reproduced in [box 1](#).

Recommendations on the height of fever appear in the clinical assessment section of the guideline. Users of the guideline will be familiar with the traffic light table that is used to stratify the risk of serious illness in this section. Body temperature does not appear in the traffic light table for children over the age of 6 months because of its poor predictive value. Children aged <6 months with temperature >39°C appear in the amber section of the table because of a moderately increased risk in this group. Children under the age of 3 months with fever are considered to be at high risk of serious illness and are therefore in the red section. This is partly because of the higher predictive value of fever in this age

### Box 1 The National Institute for Health and Care Excellence recommendations on fever and antipyretic interventions

#### Assessment of risk of serious illness

- ▶ In children older than 6 months, do not use height of body temperature alone to identify those with serious illness.
- ▶ Recognise that children aged 3–6 months with a temperature of 39°C or higher are in at least an intermediate-risk group for serious illness.
- ▶ Recognise that children younger than 3 months with a temperature of 38°C or higher are in a high-risk group for serious illness.

#### Antipyretic interventions

- ▶ Antipyretic agents do not prevent febrile convulsions and should not be used specifically for this purpose.
- ▶ Tepid sponging is not recommended for the treatment of fever.
- ▶ Children with fever should not be underdressed or overwrapped.
- ▶ Do not use antipyretic agents with the sole aim of reducing body temperature in children with fever.
- ▶ Consider using either paracetamol or ibuprofen in children with fever who appear distressed.
- ▶ When using paracetamol or ibuprofen in children with fever:
  - continue only as long as the child appears distressed
  - consider changing to the other agent if the child's distress is not alleviated
  - do not give both agents simultaneously
  - only consider alternating these agents if the distress persists or recurs before the next dose is due.

group but also because many studies have reported that an age of <3 months is an independent risk factor in itself.<sup>1 12 13</sup> Moreover, during the production of the guideline, we obtained information from UK Hospital Episode Statistics that showed that the risk of serious illness is >10 times greater in infants under the age of 3 months compared with that in older children presenting with fever.<sup>1</sup>

The guidance on the use of antipyretics is based on the lack of evidence for antipyretics being of use for anything other

than reducing body temperature and acknowledging that this effect is not necessarily of benefit to the child. We have therefore encouraged a stepwise approach to the use of antipyretic agents; only proceeding to the next step if there has not been an adequate response to the earlier agent. It is gratifying to note that our guidance on antipyretic agents is remarkably similar to the guidance recently issued by the American Academy of Pediatrics following their own review of the evidence.<sup>34</sup>

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