

Why is the evidence not affecting the practice of fever management?

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Fever is a very common complaint in children and is the single most common non-trauma-related reason for visits to the emergency department.¹ Parents are concerned about fever and its potential complications, but what knowledge do they actually have about fever and its management at home? The biological value of fever (ie, whether it is beneficial or harmful) is disputed and fever is vigorously treated in the hope of lessening its complications. The practice of alternating two types of antipyretics has become widespread at home and on paediatric wards, but is this practice supported by evidence and does it result in complications? There is still a significant contrast between scientific evidence on the one hand and current concept and practice on the other. Why is that the case in such a common complaint as fever?

Fever is often considered by parents and doctors as a major and harmful sign of illness, almost as an illness in itself rather than a symptom. Parents worry when their child is feverish and feel that fever may spiral upwards with a possible fatal outcome. Fever phobia, an exaggerated fear of fever in their children, is common among parents.² Parents have a limited understanding of fever and little or no information about its beneficial role in diseases.³ These parental concerns lead to the increased use of antipyretics and of health services. In addition, there is often a widespread perception among paediatricians that fever is dangerous. The majority (65%) of paediatricians in Massachusetts, USA believe that fever itself could be dangerous to a child with seizures, with death and brain damage being the most serious complications.⁴

Current practice considers the liberal use of antipyretics a necessity and demands measures to abolish even a low degree of fever.⁵ Antipyretics are parents' preferred method of managing fever and there has been an increase in the preference

for their use over the past two decades from 67% to more than 90% (91% to 95%).^{6,7} Parents' antipyretic administration is often incorrect as regards both dose and frequency.⁸ Underdosing increases health service usage and encourages the use of alternating antipyretics to maintain normal temperature, while overdosing is potentially harmful. Paediatricians who work with children in hospitals have come to accept that antipyretics are often automatically prescribed on the treatment sheet for the single indication of the presence of fever. A febrile child who is playful on the ward and a child with significant discomfort due to fever both receive antipyretics. Although most paediatricians agree that treatment of a febrile child with antipyretics is mostly for the relief of the symptoms of fever, many tend to prescribe antipyretics for any child with fever. Paediatricians may be contributing to fever phobia by prescribing antipyretics for children who are only mildly febrile or by recommending the use of paracetamol alternating with ibuprofen. This practice of alternating antipyretics has become increasingly common with parents, their use rising from 27% in 2001 to between 52% and 67% in 2007.⁹ Pharmaceutical companies and the media may also be contributing to myths and fears with comments or advertisements such as "If you love your child, get rapid relief with this medicine" or "If you care about the comfort of your child use ...", etc.

It is possible that the negative views about fever have historical roots. Throughout most of history fever was feared by ordinary people as a manifestation of punishment induced by evil spirits or as a marker of death.^{10,11} However, Wagner von Jauregg in 1917 gave enormous impetus to the idea of fever as a therapeutic agent by treating neurosyphilis with malarial fever.¹² One of the most important outcomes of research in recent years has been the discovery of a single mononuclear cell product, interleukin-1 (IL-1), whose effects include induction of fever and activation of T lymphocytes.¹³

Numerous substances from outside the body (exogenous pyrogens) can initiate the fever cycle. Endotoxins of Gram-negative bacteria are the most potent exogenous pyrogens. The exogenous pyrogens stimulate monocytes, fixed-tissue macrophages and reticuloendothelial cells to produce and release endogenous pyrogens, of which IL-1 is the most important. IL-1 acts on the hypothalamic thermoregulatory centre through mediators, particularly PGE₂, to raise the thermostatic set-point. The hypothalamic centre stimulates heat production by inducing shivering and heat conservation through vasoconstriction. Fever is regulated by this centre (even at a temperature of over 41°C) and heat production approximates loss, as in health, although at a higher level of the set-point. IL-1 has other functions, including:

- ▶ playing a primary role in the induction of inflammatory responses, such as neutrophil accumulation and adherence, and vascular changes;
- ▶ stimulating the liver to synthesis acute-phase proteins such as fibrinogen, haptoglobin, ceruloplasmin and CRP;
- ▶ initiating T cell and B cell proliferation and activation (IL-1 activates T lymphocytes to produce various factors, such as INF and IL-2, which are vital for immune response).

The production of fever simultaneously with lymphocyte activation strongly suggests fever has positive role.

But is fever actually beneficial or is it harmful? Fever per se is self-limiting and rarely serious provided that the cause is known and fluid loss is replaced. With fever, unlike hyperthermia, body temperature is well regulated by a hypothalamic set-point that balances heat production and heat loss so effectively that the temperature does not increase relentlessly above an upper limit of 42°C. Within the range of 40°C to 42°C, there is no evidence that fever is injurious to tissue. About 20% of children seen in the emergency room have temperatures over 40°C, but they almost always recover fully and any morbidity or mortality is due to underlying disease. Indeed, the associated fever may well be protective. Fever should not be regarded as harmful for the following reasons:

- ▶ Fever exerts an overall adverse effect on the growth of bacteria and the replication of viruses.^{14,15} It enhances immunological processes, including

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the activity of IL-1, T helper cells and cytolytic T cells, and B cell and immunoglobulin synthesis.¹⁶ Fever may also be beneficial in febrile children with meningitis compared to those who are afebrile or hypothermic, who were reported to have died.¹⁷ A study of 102 children with salmonella gastroenteritis from Finland¹⁸ demonstrated a significant negative correlation between the degree of fever and the duration of excretion of organisms.

- ▶ There is now abundant evidence that antipyretics do not prevent febrile seizure.¹⁹ Children with a high risk of recurrence of febrile seizure (positive family history of febrile seizure, age <1 year, complicated febrile seizure, and low grade fever at the onset of febrile seizure) have frequent recurrences compared with those without these risk factors. As antipyretics are used for both groups of children, it may be the risk factors, and not the antipyretics, which predispose to recurrences. Numerous studies have shown that children who develop seizures with lower degrees of fever have a lower seizure threshold and therefore a high recurrence rate of febrile seizure, while those with high fevers over 40°C have fewer recurrences.²⁰⁻²²
- ▶ The hygiene theory suggests that fever may be beneficial. The prevalence of asthma and allergies has increased worldwide for many years and the hygiene theory has been offered as an explanation.²³⁻²⁴ The theory proposes that early exposure to infections, often associated with fever, might protect children against allergic diseases. The following findings support this theory:
 - The prevalence of atopy is lower among children of large families and those attending day-care nurseries than among children of small families or those not attending nurseries.
 - Children with older siblings are less likely to develop allergies than children with younger or no siblings.
 - Atopic diseases are rare in countries with parasitic infestation.

If fever is considered beneficial, we might expect that antipyretics could have a harmful effect:

- ▶ Antipyretics are known to cause adverse reactions, such as gastrointestinal bleeding and renal failure, and some fatalities.²⁵⁻²⁶ In the UK, 10% of

inquiries to the National Poisons Information Service and up to 43% of all admissions to hospital with self-poisoning are due to paracetamol.²⁷⁻²⁸ In the USA, paracetamol-associated overdoses account for 56 000 emergency visits and 26 000 hospitalisations, with approximately 450 deaths each year. About 100 of these deaths are unintentional.²⁹

- ▶ In human volunteers infected with rhinovirus, the use of antipyretics was associated with suppression of serum antibody response, increased symptoms and signs and a trend towards longer duration of viral shedding.³⁰ In a study of children with chickenpox (half of whom received paracetamol four times a day and half of whom received a placebo) the time to total scabbing was slightly shorter in the placebo group (5.6 days) than in the paracetamol group (6.7 days).³¹ Another study from Japan³² found that the frequent administration of antipyretics to children with bacterial diseases led to a worsening of their illness.
- ▶ Fever is a valuable physical sign in a number of conditions such as Kawasaki disease and juvenile idiopathic arthritis. Antipyretics may modify diagnostic fever patterns in these conditions and make diagnosis more difficult.
- ▶ A Cochrane review concluded there is insufficient evidence that paracetamol has a superior effect compared to placebo alone.²⁰

Despite the controversy on the subject, paediatricians should agree on the following points:

- ▶ The accumulated data now suggest that fever has a protective role in promoting host defence against infection rather than being a passive by-product. A moderate fever (less than 40°C) is beneficial.
- ▶ The principal benefit of antipyretic drugs is to make children more comfortable and relieve parents' anxiety.
- ▶ Febrile seizure is usually benign and does not cause brain damage. Its prevention is difficult and may not be achievable with antipyretics.
- ▶ Evidence-based educational interventions are the best way to treat and prevent fever phobia and reduce the unnecessary use of health services. This information is best delivered during routine health checks, as parents' anxiety may interfere with their understanding of facts presented when their child is sick. Parents

should be taught how simply to assess the child's well-being (eg, skin colour, activity levels, respiratory rate and hydration). The media has an important role in contributing to the instruction and education of caregivers.

- ▶ Antipyretics should be used with indications, like other drugs, and not for fever per se.

Fever management may involve standard therapeutic intervention in the following situations:

- ▶ where the child has symptoms such as pain, discomfort, delirium or excessive lethargy. Antipyretics serve here to improve the child's well-being, allowing them to take fluids, and to reduce parental anxiety.
- ▶ where there is limited energy supply or increased metabolic rate (eg, burn, cardiovascular and pulmonary diseases, prolonged febrile illness, very young age, undernourishment, and postoperative state). Fever can increase the metabolic rate and may aggravate disease.
- ▶ where young children are at risk of hypoxia because of an acute respiratory condition such as bronchiolitis. The presence of fever may increase oxygen requirements and worsen disease.³³
- ▶ where there is high fever of over 40°C, for the following reasons:

- Children with such high fever have rarely been studied.
- Children with such high fever are likely to be symptomatic and at high risk of dehydration and delirium.
- Not advocating antipyretics for such high fever would cause dismay among parents and controversy among paediatricians, who may consider such a recommendation unethical.

We should not support the following interventions:

- ▶ antipyretics for the substantial proportion of febrile children with minimal or no symptoms. Such a recommendation may initially upset parents as they may consider that their sick child is not being treated. But if we are to lead in our fields, we should help to educate the public about the results of research.
- ▶ physical measures such as the use of a fan or tepid sponging. These are unnecessary and unpleasant interventions

for the child.^{34 35} Their main indication is hyperthermia.

- ▶ alternating antipyretics (paracetamol and ibuprofen). There is no evidence to support this practice according to a Medline search of the literature from 1970 to 1998.³⁶ Alternating antipyretics can be confusing for caregivers, potentially leading to incorrect dosing of either product. The practice can also increase parents' fever phobia as it increases parental preoccupation with the height of the fever. Furthermore, a fever reduction of 0.5°C when combining antipyretics compared with a single antipyretic is insufficient to warrant routine use.³⁷

Although there is evidence to support the positive effects of fever, whether fever is beneficial or not is still controversial. We need to know which diseases are likely to benefit from the presence of fever, so that minimal interference during their courses may be considered. On the other hand, we should investigate in which diseases associated fever and to what degree it may be harmful so that steps can be taken to treat it.

Finally, research indicates that we are at a crossroads between strong research evidence accumulated during the past few decades supporting a positive role of fever and the continued pressures of current practice to lower body temperature. When we focus upon "treating" fever, we are giving the impression to parents and health professionals that fever is harmful and antipyresis is beneficial. Scientific evidence does not support this practice. To continue the current liberal use of antipyretics may mean that we are ignoring important messages from research.

Competing interests: None.

Accepted 23 May 2008

Published Online First 18 June 2008

Arch Dis Child 2008;**93**:918–920.
doi:10.1136/adc.2008.139949

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Arch Dis Child 2008 93: 918-920 originally published online June 18, 2008

doi: 10.1136/adc.2008.139949

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