Fever management: Evidence vs current practice

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Abstract

Fever is a very common complaint in children and is the single most common non-trauma-related reason for a visit to the emergency department. Parents are concerned about fever and it’s potential complications. The biological value of fever (i.e., whether it is beneficial or harmful) is disputed and it is being vigorously treated with the belief of preventing complications such as brain injury and febrile seizures. The practice of alternating antipyretics has become widespread at home and on paediatric wards without supporting scientific evidence. There is still a significant contrast between the current concept and practice, and the scientific evidence against such concepts and practice.

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Key words: Acute childhood illnesses; Fever phobia; Physicians; Febrile seizure

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CURRENT CONCEPTS AND PRACTICE

THAT FEVER IS HARMFUL

Current concepts among parents

Acute childhood illnesses are often associated with fever, which is considered by parents and by many doctors as a major and harmful sign of illness, sometimes as an illness itself rather than a symptom and a host defense response. Parents worry when their child is feverish and feel that fever may spiral upwards with a possible fatal outcome. As a result, they are convinced that antipyretic measures must be used to lower fever. Fever phobia, an exaggerated fear of fever in their children, is common among parents[1,2]. Parents have a poor understanding of fever and little or no information about its beneficial role in diseases[3]. As antipyretics do not normalize body temperature or prevent recurrences of fever, parents’ concerns increase leading to increased use of antipyretics and health services. Pharmaceutical companies and the media may also be contributing to myths and fears of fever 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 this medicine”, etc. By giving children the antipyretic medication the child soon feels better. The parent is then relieved that the lowered fever is the cause of the improvement in her/his child. But, this is most likely simply due to the reduction in pain and discomfort caused by the medication (see below).

Current concepts among physicians

There is often a wide perception among pediatricians that fever is dangerous. The majority (65%) of pediatricians in Massachusetts, USA, believe that fever itself could be dangerous to a child with seizures; death and brain dam-
age being the most serious complications of fever if the temperature is 40 °C or greater[3]. Although most pediatricians 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. Pediatricians 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. The biological value of fever (i.e., whether it is beneficial or harmful) is disputed among physicians and it is being vigorously treated with the belief of preventing its complications.

**Risk of febrile seizure**

Febrile seizure (FS) has been one of the diseases where antipyretic treatment has strongly been advocated. In a study from the USA, 49% of pediatricians considered convulsions to be a principal danger of fever and 22% believed that that brain damage could result from typical FS[8]. Early literature reported a mortality rate of 11% in children with FS[8].

As fever is generally considered to be an essential precursor of a FS, medical professionals have concluded that antipyretic measures should prevent febrile seizures. Antipyretics continue to be among the most commonly prescribed medications, especially for children at risk of such seizures. Parents are usually advised that the administration of antipyretics to at-risk child may reduce the risk of further convulsions.

The current practice considers the liberal use of antipyretics a necessity and demands measures to abolish fever, even for a low degree of fever[7]. Antipyretics are parents’ preferred method of managing fever and there has been an increase in this preference over the past two decades from 67% to more than 90% (91% to 95%)[2,8,9]. Of concern to health professionals is that parents’ antipyretic administration is often incorrect both in dose and frequency[10,11]. Underdosing increases health service usage and encourages alternating antipyretics to maintain normal temperature. Overdosing is potentially harmful. The practice of alternating antipyretics has become widespread on pediatric wards and doctors are not sure whether this practice is supported by evidence and are there complications as a result. Parents reported to use this practice rising from 27% in 2001 to between 52% and 67% in 2007[12]. Pediatricians who work with children in hospitals have come to accept that antipyretics are very often automatically prescribed on the treatment sheet for the single indication, that is, 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.

It is possible that the negative views about fever have their roots historically. Throughout most of history fever was feared by ordinary people as a manifestation of punishment, induced by evil spirits or a marker of death[13]. Claude Bernhard (1813-1878), the great French physiologist, recognised that body temperature was regulated in healthy organisms by the balancing of heat production and loss. He demonstrated that animals died quickly when the body temperature exceeded the normal level by 5-6 °C, thus suggesting that fever may be harmful and that antipyretics, which were introduced later, may be beneficial[16]. William Osler (1849-1919) declared that ‘the humanity has three enemies, fever, famine and war, but fever is by far the greatest’.

**EVIDENCE THAT FEVER IS BENEFICIAL**

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 climb up relentlessly and does not exceed an upper limit of 42 °C. Within this upper range, 40 °C to 42 °C, there is no evidence that the fever is injurious to tissue. About 20 percent of children seen in the emergency room have temperatures over 40 °C but they usually have a full recovery. If there is morbidity or mortality, it is due to the underlying disease. The associated fever may well be protective.

**Furthermore**

Fever exerts an overall adverse effect on the growth of bacteria and on replication of viruses[18]. It also enhances immunological processes, including activity of interleukin-1 (IL-1), T-helper cells, cytolytic T-cells, B-cell and immunoglobulin synthesis[17]. The mobility, phagocytosis and killing of bacteria by polymorphonuclear leukocytes are significantly greater at temperatures above 40 °C. Elevated temperatures of 38 °C and 39 °C have a direct positive effect on lymphocyte transformation, the generation of cytolytic cells, B-cell activity, and immunoglobulin synthesis[18]. IL-1 is more active at febrile temperature than at an afebrile temperature. Interferon (INF), a potent antiviral agent, has enhanced antiviral activity above 40 °C[19].

Human studies are also in support that fever may be beneficial. Fever was the principal form of treatment for syphilis and gonorrhoea about a century ago. A study from Japan[20] found that the frequent administration of antipyretics to children with bacterial diseases led to a worsening of their illness. A study of 102 children with salmonella gastroenteritis from Finland[21] demonstrated a significant negative correlation between the degree of fever and the duration of excretion of organisms. In a series of children presenting with severe infection, such as pneumonia or septicaemia, it was found that the lower the body temperature, the higher the mortality[22,23]. Insufflations of humidified air at 43 °C (three 30-min sessions at 2-3 h intervals) into the nasal passages of patients suffering from coryza resulted in the suppression of symptoms in 78% of patients [23]. 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[34]. In a study of children with chickenpox, half of whom received paracetamol four times a day, and half received a placebo, the time to total scabbing was slightly shorter in the placebo group (5.6 d) than in the paracetamol group (6.7 d)[23].

Concerning the risk of FS, there is now abundant evidence indicating that antipyretics have no effect on preventing further FS[26]. Children with high risk of recurrences of FS (positive family history of FS, age < 1 year, complicated FS, low grade fever at the onset of FS) develop frequent recurrences while those without these risk factors rarely develop recurrences. Antipyretics are used for both groups of children, suggesting that it is the risk factors, and not the antipyretics, which predispose to recurrences. Several randomized, placebo-controlled trials on children at risk of FS found no evidence that the antipyretic paracetamol or ibuprofen, with or without diazepam, was effective in preventing FS during subsequent febrile episodes[27,28,29]. Furthermore, numerous studies show that a temperature > 40 °C is associated with decreased incidence of recurrence while children who develop seizures with lower degrees of fever have lower seizure threshold and therefore high recurrence rate of FS[30]. Thus, a high temperature at the onset of FS is a useful predictor of non-recurrence. Furthermore, a Cochrane review concluded that the evidence that paracetamol has a superior effect than placebo is insufficient[31].

Antipyretics are known to cause adverse reactions and some fatalities. In the UK, paracetamol has been one of the most popular choices for suicide attempts in adolescents and adults, causing 100-150 deaths annually. In the USA, paracetamol-associated overdoses account for 56,000 emergency visits, 26,000 hospitalizations, with approximately 450 deaths each year. About 100 of these deaths are unintentional[32].

The benefits of fever may also be found in the hygiene theory. The prevalence of asthma and allergies has increased worldwide for many years and the hygiene theory has been offered to explain the rise[33]. The theory proposes that early exposure to infections might protect children against allergic diseases.

**In support of this theory are the following findings**

The prevalence of atopy is lower among children of large families or those attending day-care nurseries than among children of small families or those not nurseries. Children with older siblings are less likely to develop allergies than children with younger siblings or none at all. Atopic diseases are rare in countries with parasitic infestation.

**Benefits of fever are found among ancient scholars**

The Hippocratic writings contain evidence that fever was thought to be beneficial to the infected host, “fever was beneficial in ophthalmia” and it cured it[34]. Since Hippocrates believed in the benefit of fever, he placed little emphasis on the treatment of it. When a disease was caused by an excess of one of the four bodily humors, the excess humour was then “cooked”, separated and removed by the fever. Rufus of Ephesus, a surgeon who lived at the beginning of the 2nd century AD, strongly advocated the beneficial role of fever. He was the first physician to recommend the use of “fever therapy”, such as by malarial fever, to treat epilepsy. He said: “fever is a good remedy for an individual seized with convulsion, and if there were a physician skilful enough to produce a fever it would be useless to seek any other remedy against disease[35]. For Thomas Sydenham (1624-1689), he clearly regarded fever as beneficial as witnessed by his remark “fever is a mighty engine which nature brings into the world to remove her enemies”[36].

**More recent evidence**

It was Wagner von Jauregg in 1917 who gave an enormous impetus to the research with his work that fever was an effective treatment of neurosyphilis with malarial fever[37]. One of the most important outcomes of this research in recent years has been the discovery of a single mononuclear cell product, IL-1, whose effects include induction of fever and activation of T-lymphocytes. Numerous substances from outside the body, exogenous pyrogens (ExPs), initiate the fever cycle. Endotoxin of Gram-negative bacteria is the most potent ExPs. The ExPs 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 center through mediators, particularly PGE2, to raise the thermostatic set-point. The hypothalamic center accomplishes heat production by inducing shivering and heat conservation through vaso-constriction. At an established degree, fever is regulated by this centre (even at a temperature of about 41.0 °C) and heat production approximates loss, as in health, though at a higher level of the set-point. Therefore fever does not climb up relentlessly. 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 certain proteins, acute-phase proteins, such as fibrinogen, haptoglobin, ceruloplasmin and CRP. 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 constitutes the clearest and strongest evidence in favour of the role of fever.

**RECOMMENDED FEVER MANAGEMENT**

**Education**

Health professionals should consider parental education as the core of fever management with the objective to improve parental knowledge and anxiety and to reduce
unnecessary use of health services. The following advice may be given: Fever is normal part of the body response to fight the infection; The body temperature is well controlled in the brain and does not rise relentlessly. This is in contrast to hyperthermia (e.g., heat stroke) where the body temperature may exceed 42.0 °C; Euthermia is not an objective of antipyretic treatment, but make the child comfortable is so; How sick the child looks (e.g., drowsy, lethargic, not playful, not smiling) is more important than the level of the fever; The primary objective of any antipyretic intervention is to decrease the child’s discomfort; Antipyretic drugs such as paracetamol should not be used automatically for any fever and their use needs to be balanced against any harm that might result from this intervention. They have side-effects and should be used cautiously and according to the instruction prescribed; Paracetamol is an effective antipyretic and analgesic and a long history of safety. It should remain the drug of choice to use for febrile children. Ibuprofen has a significant potential side-effects; Sudden fever may cause a harmless “febrile seizures or convulsion in 3%–5% of those genetically susceptible children. The seizure does not cause brain damage. Fever-reducing medicines, even prophylactically, does not prevent further seizures.

**Therapy is indicated for following situations**

Symptoms such as pain, discomfort, delirium, excessive lethargy. Antipyretics serve here to improve the child’s well-being, allowing the child to take fluid and reduce parental anxiety.

A situation associated with limited energy supply or increased metabolic rate (e.g., burn, cardiovascular and pulmonary diseases, prolonged febrile illness, young children, undernourishment, and postoperative state). Fever can increase the metabolic rate and exert a harmful effect on the disease.

Young children who are at risk of hypoxia because of acute respiratory condition such as bronchiolitis, since the presence of fever may increased oxygen requirement and worsen the disease.[38]

A high degree of fever > 40 °C for the following reasons: Children with this high degree of fever have rarely been studied; Children with this high degree of fever are likely to be symptomatic and at potentially high risk dehydration and delirium; Not advocating antipyretics for this high degree, would cause controversy among paediatricians and dismay among parents.

We should not be in support of the following interventions: Antipyretics for a child who does not have one of the above conditions, that is a febrile child with minimal or no symptoms such as discomfort. This constitutes a substantial proportion of febrile children. Such a recommendation may initially cause some dismay among parents because of their perception that their sick and needy children are not being treated. But, if we are to play a leadership role in our fields, we should help to educate the public about the results of research; Physical measures such as a fan or tepid sponging are discouraged. These are unnecessary and unpleasant for the child. Their main indication is hyperthermia; The practice of alternating antipyretics (paracetamol and Ibuprofen) should be discouraged for there is no evidence to support this practice. The practice can also increase parents’ fever phobia as it increases parental preoccupation with the height of the fever.

**CONCLUSION**

Despite the controversy of the subject, paediatricians could reach a consensus on the following concepts: 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 the antipyretic drug is to make children more comfortable and to relieve the parents’ anxiety. Febrile seizures are usually benign and does not cause brain damage. Its prevention is difficult and may not be achievable. Antipyretics can not prevent FS. Evidence-based educational interventions are the best way to treat and prevent fever phobia and reduce 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 wellbeing (e.g., skin colour, activity levels, respiratory rate, and hydration). Media and the magazines have an important role in contributing to instruction and education of caregivers.

Antipyretics should be used with indications, like other drugs, and not for fever per se. Although there is evidence to support the beneficial effects of fever, we should recognize that the issue as to 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 the associated fever may be harmful so that steps are taken to treat it. Also it should be determined what degree of fever is harmful and thus ought to be reduced. Finally, research indicates that we are at a crossroads, divided 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” the fever, we are giving the impression to parents and health professionals that fever is harmful and that antipyresis is beneficial. Scientific evidence does not support this practice. To continue the current practice of liberal use of antipyretics may mean that we are ignoring important messages from research.

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