Fever: to treat or not to treat?

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Fever

Fever is the chief complaint in up to one third of all pediatric office visits. The pathophysiology of this condition is relatively well defined. Body temperature is regulated by thermo-sensitive neurons, located in the pre-optic or anterior hypothalamus, which respond to change in blood temperature as well as to direct neural connections with cold and warm receptors located in skin and muscle.[1] Various infectious toxins and inflammatory products resulting from the body's immunologic response induce the production of endogenous pyrogens by host inflammatory cells. These include the cytokines interleukin 1 (IL-1) and IL-6, tumor necrosis factor-gamma (TNF-gamma), interferon-beta (IFN-beta) and IFN-gamma.[2] The circumventricular organ system consists of neuronal tissues lying outside the blood-brain barrier that has a key role in initiating the communication sequence responsible for the synthesis of febrile prostaglandins. When pyrogenic cytokines are detected by the circumventricular organ system, prostaglandin synthesis, especially cyclooxygenase-dependent prostaglandin E2, is induced, activating the febrile response.[3] Neuronal transmission from the hypothalamus leads to conservation and generation of heat, thus raising core body temperature.[4] In humans increased temperature is associated with decreased microbial reproduction and increased inflammatory response. Evidence suggests that fever is an adaptive response and should be treated only in selected circumstances.[5] The fact that the hypothalamic set-point is reset by the inflammatory response could be one of the reasons that physical methods of antipyresis are relatively ineffective.[6] However major texts still quote physical methods as being useful in febrile children.[7]

Fever is a normal adaptation to a pyrogenic stimulus. It differs from hyperpyrexia and hyperthermia which are associated with hot environments[8] and pharmacological triggers[9] and which tend to respond poorly to conventional pharmacological antipyresis. Fever increases insensible losses through increased sweating[10] as well as leading to increased oxygen consumption, carbon dioxide production and cardiac output.[7,11] Studies on the adaptive value of fever demonstrate an association between a rise in body temperature and a decrease in mortality and morbidity during infection.[5,12] It has been suggested that fever has evolved as a host defense mechanism which has been preserved through hundreds of millions of years of evolution.[13]

Fever phobia

Fever phobia is a persistent problem and caregivers continue to be 'very worried' about fever, their main concerns being possible central nervous system damage (24%), seizures (19%) and death (5%).[14] Pediatric health care providers are uniquely situated to be able to make an impact on parental understanding of fever and its role in illness[15] by providing clear and authoritative information.

The body does not allow lethal temperature to occur as long as there is no dehydration, and an open environment is provided to allow for heat loss.[16,17] The rare exception to this is when there is an underlying neurological condition affecting the temperature control centre, e.g., hypothalamic lesion. Furthermore, fever is purposeful and protective.[16,18]

Although fever is associated with febrile seizures, it is well established that this condition, which occurs in 5% of children between the age of six months and five years, is benign, with a normal cognitive outcome, and a low risk of epilepsy.[19] Febrile seizures may be more likely to occur with rapid rises in temperature[20] as may occur at the onset of febrile illnesses or with rapid antipyresis, e.g., alcohol sponging, however not all authors agree with this observation.[21] Some authors relate the febrile seizure to the height of the fever.[22]

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One third of all children who have a febrile seizure will have a second episode despite vigorous attempts at prevention with antipyretics.[23]

Anticonvulsants have been somewhat effective in preventing recurrence of febrile seizures but side effects preclude their use.[24]

Primum non nocere

Primum non nocere, "First, do no harm", is one of the principal precepts taught to medical students. It reminds the physician that he or she must consider the possible harm that any intervention might cause, and stresses that human acts with good intentions may have unwanted consequences. Since fever is not in itself harmful, and may even be protective, there is no particular reason to treat it other than as a comfort measure. Although the lack of response to antipyretics does not necessarily imply that infection is more serious or significant, the resumption of active play and interaction with the environment after successful antipyresis indicates that dangerous causes of fever are less likely. However caution should be exercised when considering conditions with cyclical fever such as malaria.

If fever is harmless, and may actually be beneficial, the question becomes: is it harmless to treat fever? There are significant risks to the treatment of fever.

(1) Nosocomial infections: When parents seek medical help from a health care practitioner there may be an unavoidable risk of their child contracting a nosocomial infection from others waiting to see the physician.

(2) Inappropriate focus: Fear of fever and inappropriate concentration on the need to treat it could side track parents, and even some physicians, from the more important signs of serious illness.[25]

(3) Poisoning: Inappropriate use of antipyretics by both physicians and parents can lead to intoxications. A study performed in a busy pediatric emergency department revealed a 10.1% incidence of drug error by physicians, the most common significant error involving acetaminophen.[25] Heubi et al[26] reported acetaminophen hepatotoxicity after multiple overdoses from published cases: 47 children (aged 5 weeks to 10 years) received 60 to 420 mg/kg per day for 1 to 42 days, and 24 died. In another study Rivera-Penera et al[27] reviewed the medical records of 73 pediatric patients admitted for acetaminophen overdose. Twenty-eight patients (39%) had severe liver toxic effects, six of whom underwent liver transplantation. Multiple miscalculated overdoses, given by parents, were a risk factor and the major cause of overdose in children of 10 years old or younger.[27] Non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen are known to have adverse effects on kidney function. The use of NSAIDS in situations where the renin-angiotensin system is stimulated, such as volume depletion or preexisting chronic renal failure predisposes to acute renal failure via inhibition of prostaglandin synthesis.[28] Ulinski and Bensman[29] reported a series of children, presenting with diarrhea and/or vomiting and fever, treated with therapeutic doses of ibuprofen (11.5-32 mg/kg per day) for 1-3 days, who went on to develop acute renal failure. Maximum plasma creatinine levels were 180-650 pmol/L and one patient required emergency dialysis for hyperkalemia, uremia, and hyperphosphatemia. Aspirin is of course no longer recommended for routine antipyretic use in children because of its potential to cause gastrointestinal bleeding and Reye's syndrome.[30]

The practice of combining or alternating ibuprofen and acetaminophen has become common, but may confuse parents and once again inappropriately stresses the need to treat fever. Alternating doses have been shown to be slightly more efficacious in controlling temperature.[31,32]

What should we do?[33]

Parents and even physicians need to be educated that:

(1) There is a need to concentrate on the *cause* of the fever, *not its treatment.*

(2) Fever may actually be beneficial in fighting infection.[34]

(3) A child can have meningitis with a low fever, or a viral upper respiratory tract infection with a high fever. The difference is that the child with meningitis will look and behave in a much more ill fashion.

(4) Minimal clothes and a cool environment are a good non-medicinal way to treat fever.

(5) Children with fever must be kept well hydrated.

(6) Treatment of fever can be dangerous, and correct dosing regimens must be learnt and observed, namely: acetaminophen 15 mg/kg four hourly but *not more than five times* a day so as not to exceed the recommended daily limit of 80 mg/kg per day. In some countries the total recommended daily dose has recently been reduced to as little as 60 mg/kg per day.[35]

(7) There is no advantage to giving bigger doses, even if the rectal route is used.[36]

(8) Ibuprofen can be given in doses of 10 mg/kg six hourly.

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