Fever: Measuring and Managing

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In Brief

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At least in Western cultures we have a strong tradition of viewing fever not only as a response to illness but also as a disease itself. Although our science teaches us that fever, as part of the inflammatory response, is only a sign or symptom of the real pathologic process, our nomenclature (blackwater, cat scratch, dengue, hay, jungle, puerperal, rat bite, relapsing, rheumatic, Rocky Mountain spotted, scarlet, typhoid, and yellow fever) reinforces the temptation to treat fever as if it were the noxious culprit itself. Fever, as opposed to hyperthermia, rarely poses a threat to a child's well-being; in fact, as an energy-expensive phenomenon, fever is not likely to have weathered evolution without conferring some survival benefit. Considering that fever is the most common signal of illness in children, serving as the cause of as many as a third of all pediatric office visits, we would do well to clarify our approach to its management that is distinct from the illnesses that cause it.

Fever is a regulated elevation of body temperature, mediated by the anterior hypothalamus, which occurs in response to any insult that stimulates the body's inflammatory defenses. Similar to a thermostat, the hypothalamic set point controls the temperature the body tries to maintain. Some provocation, in children most commonly a viral infection, induces macrophages to release cytokines that function as endogenous pyrogens. They circulate to the anterior hypothalamus, where they increase local levels of prostaglandin E_2 and induce an increase in the set point. Several mechanisms then come into play to bring the core temperature (the temperature of blood within the pulmonary artery) up to the new set point. Because the core temperature as it begins to elevate is lower than the thermostat setting, a person developing fever feels chilled. Physiologically, the body's response is to generate more internal heat, setting skeletal muscles to shivering and stimulating cellular metabolism, while minimizing heat loss by vasoconstricting the skin and turning off sweat glands. The one strategy is analogous to heating up the furnace, the other to closing the windows.

Hyperthermia, on the contrary, is an unregulated increase in core temperature to a level above the hypothalamic set point from overproduction of heat (thyroid storm), a reduced ability to dissipate heat (a bundled-up infant), or a combination of both (heat stroke from overexertion on a hot and humid day). The body's response to hyperthermia is the opposite of its response to fever: instead of an initial chill, intense flushing results from blood vessels vasodilating and sweat glands activating to lose as much heat as possible to the outside. With the furnace burning out of control, the strategy is to open the windows wide.

Whereas hyperthermia may increase body temperature to dangerous levels, fever is a homeostatic process, physiologically regulated within benign limits. It is unusual, even for patients with untreated serious infections, to have a temperature greater than 106°F (41.1°C), often termed *hyperpyrexia*. Studies of large numbers of children coming to emergency departments have consistently found that only approximately 0.05% have a temperature greater than 106°F (41.1°C). Although it seems true that the higher a temperature the greater the risk of a serious bacterial infection, even with a temperature of 106°F (41.1°C) viral illness is far more common, and no evidence suggests the elevated temperature itself poses a threat to an otherwise healthy child except in the extraordinarily rare event that the temperature exceeds 107°F (41.7°C). A child with a temperature greater than 106°F (41.1°C) is likely to have an element of hyperthermia, such as dehydration, in addition to fever. As an intrinsic

feature of the febrile response, the body releases endogenous cryogens, peptides that counterbalance pyrogens and modulate how high the hypothalamus sets its thermostat.

As a centrally regulated response to an inflammatory insult, fever is a component of the body's acute phase reaction and is an adaptive response widely present in the animal kingdom. Even among cold-blooded species, some fish and lizards, when infected, move to a warmer part of their environment, thus increasing their body temperatures. This behaviorally induced fever has demonstrable survival benefit, which can be negated with antipyretic agents. Fever retards the growth of many pathogenic microorganisms, both viral and bacterial, and limits the availability of iron, which many invasive bacteria require for survival; it enhances neutrophil migration and the production of superoxides, promotes T-cell proliferation, and increases the activity of interferon. Its metabolic cost argues for fever playing some protective role in the infected host: a process that results in a 7% to 10% increase in energy expenditure for each 1°C increase in temperature is not likely to have persisted so widely in nature for millions of years without conferring some survival benefit.

If, then, fever itself only rarely poses a threat to a child and may even be of benefit, why are parents and pediatricians so generally aggressive about treating it? In a classic study, Schmitt coined the phrase *fever phobia* when he described the prevalence of parents' misunderstanding about fever: almost every parent thought fever could cause harmful effects, with 46% fearing permanent brain damage, 58% describing a temperature greater than 102°F (38.9°C) as *high,* and 16% actually believing that if left untreated temperature might increase to 110°F (43.4°C) or higher. Given these responses, not surprisingly 63% of parents worried "lots" about the harm fever might cause their children, and 56% gave antipyretics for a temperature within the normal range. Half the parents reported that physicians or nurses were their most important source of information about fever. This claim was given credence by a survey of members of the American Academy of Pediatrics in Massachusetts in which two-thirds believed fever itself can pose a danger to children and routinely recommended treatment for temperatures higher than 102°F (38.9°C), and one-fourth cited death and brain damage as potential complications of temperatures as low as 104°F (40.0°C). We seem to be treating children less for their benefit than to allay our own anxieties as physicians and parents.

As would be expected with any physiologic parameter, no single normal value represents the gold standard for body temperature. Rather, a range of normal values must account for variations from person to person, fluctuations that reflect both a circadian pattern and age-related differences, and disparities arising from the method and site of measurement. Young children tend to have higher normal body temperatures than older children or adults, and body temperature is higher in the late afternoon and early evening than late at night or early in the morning, with a swing of as much as 3°F (1.7°C). The temperature cited most often as defining fever is 100.4°F (38.0°C).

Digital thermometers have replaced mercury thermometers and are available for rectal, oral, and axillary measurement. Rectal measurement offers the best approximation of core temperature and has been the standard for children in the first 3 or 4 years of life, but its accuracy can be affected by poor technique, stool in the rectum, and poor perfusion. In older children, because rectal measurement is physically and psychologically discomforting, oral temperature is generally preferred. On average, oral temperature is approximately 1°F (0.6°C) lower than rectal temperature, but the relationship is not consistent, and accuracy depends on cooperation from the child and can be affected by hot or cold foods and tachypnea. Axillary measurement, which can be used at any age, is the most convenient and least discomforting, but with an unpredictable relation to rectal temperature it is the least accurate method. Infrared thermometers are available for both tympanic and temporal artery measurement. Tympanic thermometers are not reliable for infants younger than 6 months, and for older children both incorrect placement in the ear canal and the presence of cerumen can affect accuracy. The so-called forehead thermometers are easier to use than tympanic instruments, and although the final word is not in, they may be reliable at all ages, even in newborns. Neither fever strips nor pacifier thermometers are accurate enough to be useful.

The management of fever rightly begins before a child becomes febrile. As a first step, pediatricians must recognize the role we have played in creating *fever phobia.* Our readiness to urge antipyretic drugs for any elevation of temperature must confuse parents when we tell them not to worry about fever itself. To reassure parents about fever when a child is ill is not as likely to be effective as counseling at a routine visit: fever is a natural response and is not a threat in itself, and it will not spiral dangerously out of control without treatment other than sensible care (eg, maintaining hydration and not overbundling). By emphasizing that the underlying illness is the possible danger to the child, we can educate parents about the symptoms and behaviors that should alert them to trouble and the need for medical attention.

If the source of a fever poses a threat, obviously it must be addressed, but treating the fever itself is a matter of judgment. An appropriate reason to intervene is for the comfort of the child,

and the decision to treat for comfort's sake should be based on how the child looks and behaves, not on any particular temperature threshold; many children tolerate fevers to 104°F (40.0°C) without apparent ill effect, whereas others become cranky at temperatures barely greater than 100.4°F (38.0°C). Another common justification for treatment is that reducing temperatures with antipyretics can distinguish children who appear ill only because they are febrile from children threatened by serious infections. In fact, neither the magnitude of fever reduction nor a child's clinical appearance after a dose of antipyretic reliably distinguishes serious from trivial infection. Although fever itself is benign in an otherwise healthy child with a self-limited viral illness, the metabolic stress it entails may be more than an already compromised child can tolerate. Increased oxygen consumption and insensible water loss, along with tachycardia and tachypnea, can further threaten a child who is significantly anemic, septic, or in shock, as well as a child made vulnerable by a systemic disease that strains homeostasis.

If fever is to be treated beyond routine attention to hydration and ambient conditions, the most sensible approach follows from understanding how the brain controls the body's temperature. When the hypothalamic set point rises, fever follows. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are effective antipyretics because they lower the set point back toward normal by inhibiting the synthesis of prostaglandin E_2. Among NSAIDs, aspirin should not be the drug of choice because of its association with Reye syndrome. Acetaminophen has the advantage of a long record of safety; it has almost no adverse effects, other than allergic reactions, unless ingested in toxic amounts greater than 140 mg/kg, which is at least 10-fold greater than its therapeutic dose (10-15 mg/kg). Children younger than 6 years, the group most frequently febrile, are also less susceptible than older children to liver destruction, the major risk of acetaminophen poisoning. However, epidemiologic evidence implicates acetaminophen as a factor in the increasing prevalence of asthma, and children with asthma or at risk for asthma may do best to avoid it. Concern has also been raised that acetaminophen used as prophylaxis against fever at the time of vaccination can blunt the antibody response.

At its optimal dose (10 mg/kg), ibuprofen reduces fever at least as effectively as acetaminophen, and with a longer duration of action it can be given every 6 rather than every 4 hours. Typical of NSAIDs, ibuprofen can cause gastritis and gastrointestinal bleeding and inhibit platelet function. NSAIDs can also cause nephropathy, certainly with long-term use, and some evidence suggests even in the short term. Ibuprofen's safety in infants younger than 6 months has not been established. The clinical situation determines whether ibuprofen's suppression of inflammation is desirable. In a child who is febrile with rheumatoid disease, ibuprofen offers relief that acetaminophen cannot; a child whose temperature arises from infection may do better if the inflammatory response is left intact. Naproxen, an NSAID with properties and adverse effects similar to those of ibuprofen, is available in a pediatric suspension; with its relatively long half-life, it can be given twice daily, at a dose of 5 mg/kg.

Using acetaminophen and ibuprofen in combination, either simultaneously or alternately, has become common. Although the 2 together may be more effective at maintaining a lower temperature than either drug alone, no evidence supports any clinical benefit to the combination, and the risk of toxic effects may well be increased.

As an alternative to medication, physical cooling can lower body temperature but potentially at the paradoxical cost of making the febrile child feel worse. Whereas antipyretics bring the hypothalamic set point down toward normal, damping the impulse to produce heat, physical measures, such as sponging, in effect open the windows to let heat escape without lowering the thermostat at all. As cooling begins, the hypothalamus senses wider divergence between its set point (still high) and the body's decreasing temperature. To close the gap, it stimulates the body to generate heat with muscular shivering and an increase in metabolic rate, which may well make a child feel uncomfortable, and with the set point remaining high, once the sponging is done the temperature is likely to increase again. Under some circumstances physical cooling has a place, as with a neurologically impaired child whose temperature control is aberrant. If an underlying illness gives urgency to reducing the metabolic stress brought on by fever, the combination of an antipyretic drug and cooling works more quickly than either alone and also makes physiologic sense: while cooling draws heat off, the drug lowers the set point to avert a rebound increase in temperature.

Comment: As my In Brief points out, hyperthermia is different from fever and poses a real and immediate threat to any child with heat illness. Successful treatment depends on restoring the core temperature to normal as rapidly as possible. Antipyretic medications, which work by lowering the hypothalamic set point, are not helpful because the set point is already below an increasing body temperature that has escaped homeostatic regulation. Here, physical cooling and fluid resuscitation are the mainstays of management.

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