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Fever: Parental Concerns

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Although fever is a common pediatric complaint, temperatures less than 41.7°C rarely cause neurologic sequelae such as obtundation and death. Most cases of fever in children cause no more than transient discomfort. Fever phobia is an exaggerated misconception about causes and consequences of fever and is very common among parents. Unsubstantiated parental concerns often push health care providers to overtreat fevers and further reinforce the phobia. To decrease this response, it is important to educate health care workers about thermometry, the pathophysiology of fever, the distinction between hyperthermia and fever, and safe evidence-based treatment strategies. Informed practitioners will in turn be better equipped to educate parents.

KEYWORDS Fever, fever phobia, Fever/diagnosis, Fever/therapy, Fever/complications, Anti-inflammatory agents, nonsteroidal, Body temperature regulation

Fever is not in and of itself a disease but rather a symptom of an underlying illness. The most common problems associated with fever include reversible discomfort and mild dehydration. In fact, only hyperpyrexia, with temperatures greater than 41.7°C, can cause grave complications such as obtundation, cerebral edema, or even death. Fortunately, a well-designed homeostatic balance prevents temperatures from reaching these alarming levels in healthy individuals. Yet overabundant parental angst regarding fever taxes vital health care resources. Fever accounts for more than 20% of emergency department (ED) visits, one third of office visits, and more than 50% of after-hour phone calls to private physicians [1-3].

Fever Phobia

Fever phobia is an exaggerated, unrealistic misconception about fever. Parental surveys regarding perceptions about fevers in 2001 [4] confirmed that the magnitude of the problem has not significantly improved since a prior survey in 1980 [5] despite attempts to increase parental education by physicians in this period. Forty-four percent of caregivers considered a temperature of 38.9°C to be a "high" fever, and 7% thought that a temperature could rise to more than 43.4°C if left untreated. Fifty-six percent of caregivers were very worried about the potential harm of fever in their children. Seizure, brain damage, and death were listed by 32%, 21%, and 14%, respectively, of caregivers as harmful effects of fever. Eighty-nine percent of caregivers gave antipyretics before the temperature reached 38.9°C, 27% alternated the use of acetaminophen and ibuprofen, and a startling 44% gave ibuprofen at intervals of less than 5 hours [4].

According to survey responses by health care providers, they may be reinforcing fever phobia. Sixty-five percent of pediatricians believed that fever could be dangerous to a child and 60% concluded that temperatures more than 40°C could lead to complications such as seizures, brain damage, or death [6]. Twenty-nine percent of pediatric ED registered nurses believed that permanent brain injury or death could occur from fever and 18% thought it was dangerous for a child to leave the ED if still febrile [7]. Although these surveys were restricted to specific geographies and might not be generalizable, they do raise concern. Proper parental education can only

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occur after appropriate physician and nursing education is accomplished.

Thermometry and Definition of Fever

Normal temperature is tightly controlled by the thermoregulatory center in the anterior hypothalamus and varies throughout the day, reaching its peak in the evening and nadir in the morning [8]. The daily variation is linked to sleep-wake cycles and generally fluctuates by a mean of 0.5°C in adults. Infants and young children have higher body temperatures than older children and adults due to both increased metabolic rates and greater surface areas. Children also have more pronounced diurnal variability in temperature than do adults [9].

In addition to numerous physiologic factors, mechanism and location of temperature attainment also impact thermometry. Oral readings vary by up to 0.95°C from the rear sublingual pocket to the anterior floor of the mouth [10]. In addition, oral temperatures are impacted by mastication, ingestion of cold foods [11], and by whether the mouth is opened or closed [12]. Therefore, patient cooperation is extremely important for obtaining meaningful measurements. Tympanic membrane [13,14], forehead [15,16], and axillary [17,18] temperatures are highly variable and imprecise. One study by Mayfield et al [19] showed axillary temperatures taken with mercury thermometers to be as reliable as rectal temperatures in newborns. However, concerns about mercury exposure when broken and difficulty reading these thermometers have decreased their popularity. Rectal temperatures are considered standard of care for infants younger than 3 months.

Often parents do not measure temperatures and only report subjective fevers. Palpation by parents has a sensitivity of 74% to 84% and specificity of 76% to 86% in children older than 2 months [20-22]. Parental palpation is not as sensitive in children younger than 2 months. Therefore, reports of tactile temperatures by parents for children older than 2 months should not be overlooked.

Fever is defined as a temperature above the reference range and is classified as a rectal temperature above 38°C, an oral temperature above 37.8°C, and an axillary temperature above 37.2°C [23]. The relationship between rectal, oral, axillary, and tympanic membrane temperatures is highly variable. There are no reliable formulas for converting readings from one site to another [11,24], and any such attempts should be done cautiously.

Pathophysiology of Fever

The febrile response is a complex reaction to disease that is characterized by activation of numerous physiologic, endocrinologic, immunologic [25], and behavioral systems. The preoptic area of the anterior hypothalamus functions as the body's thermostat by controlling thermoregulatory mechanisms that balance heat loss with heat production. The body's normal metabolic rate produces more heat than necessary to keep the set-point euthermic. Therefore, at baseline, the hypothalamic temperature control is regulating the amount of heat loss via vasodilation. When the set point rises above the body temperature, the hypothalamus activates the sympathetic system to induce vasoconstriction, increase skeletal muscle activity either as an insensible increase in muscle tone or as frank shivering, and to increase cell metabolism. This cascade of

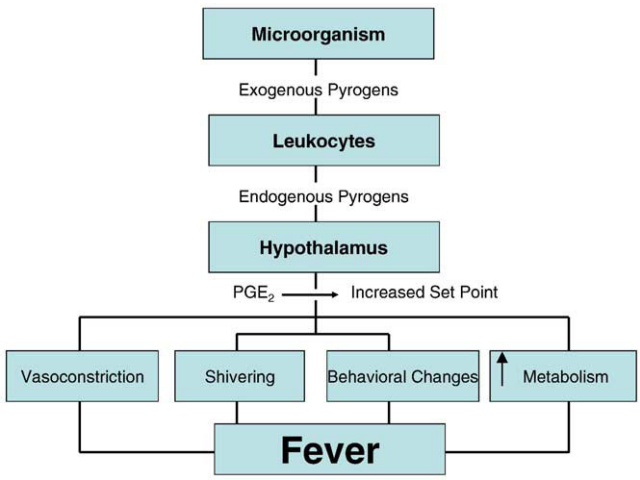

Figure 1 Pathophysiology of fever. Invading microorganisms release exogenous pyrogens that activate leukocytes to release endogenous pyrogens. These pyrogens act on receptors in the vascular organs of the hypothalamus to liberate PGE_2. Prostaglandin E_2 then raises the thermoregulatory set point that initiates the cold response. Vasoconstriction, shivering, behavioral changes, and increased metabolism ultimately raise the body temperature to the new febrile set point.

responses in turn increases core body temperature to reach the set point. Conversely, if the set point is lowered below the body temperature, hypothalamic signals cause vasodilation, sweat formation, decreased metabolism, and behavioral responses such as taking off clothing or moving to cooler environments to decrease body temperature back to its set point.

Infection by microorganisms triggers a series of events that ultimately increase the body's set point to produce fever. The invading organism releases exogenous pyrogens including lipopolysaccaride (LPS), superantigens, peptidoglycans, and muramyldipeptides that in turn activate leukocytes to release endogenous pyrogens including interleukin 1, interleukin 6, interferon-α, and tumor necrosis factor (TNF). These endogenous pyrogens, which are produced both centrally and peripherally, signal receptors in endothelial cells of the hypothalamic vascular organs to activate phospholipase A_2, which subsequently liberates prostaglandin E_2 (PGE_2) from the cyclooxygenase pathway. Prostaglandin E_2 then raises the thermoregulatory set point in the anterior hypothalamus, and the sympathetic response that ensues raises the core temperature to the febrile set-point (Figure 1).

Clinically, fever is characterized by 3 distinct phases: chill, fever, and flush [26]. During the chill phase, vasoconstriction and shivering increase the core temperature to the new thermal set point. Balance is struck between the production and loss of heat during the fever phase. Once the set point drops back down, vasodilation and diaphoresis ensue, with a flushed appearance marking the peak of the fever.

A system of checks and balances prevents temperatures from commonly exceeding 41.1°C [27]. Arginine vasopressin, α-melanocyte stimulating hormone, and TNF are endogenous cryogens that function to counterbalance the effect of pyrogens and thus prevent temperatures from rising to dangerous levels [28]. There is evidence to suggest that TNF acts both as a pyrogen and a cryogen [29]. Cryogens are produced in greater quantities during fever to curtail the magnitude and duration of fever.

To Treat or Not To Treat

It appears that fever offers the host both advantages and disadvantages. Numerous members of the animal kingdom including mammals, reptiles, amphibians, fish, and invertebrates generate a febrile response after injections of endotoxin or other pyrogenic substances [30]. Fever is an energy-expensive process; for every increase of 1°C over 37°C, there is a 13% increase in oxygen consumption [31]. If fever has such a cost to the host, then its immunologic benefit must outweigh this burden, thus withstanding evolution.

Both animal and human studies have suggested host advantages from the febrile response. Reptiles *Dipsosaurus dorsalis* infected with *Aeromona hydrophila* showed a direct correlation between body temperature and survival [32]. These findings were later confirmed in a study involving goldfish [33]. In a retrospective study of 218 human patients with gram-negative bacteremia, there was a positive correlation between maximal temperature and survival [34]. Children with chickenpox treated with acetaminophen as compared to placebo had longer time to scabbing and higher symptom scores [35]. Patients with measles had longer prodrome and delayed Koplik spot eruption when treated with aspirin as compared to placebo [36].

Disadvantages of fever include increased metabolic rate, oxygen consumption, and carbon dioxide production. Patients with underlying cardiovascular pathology or who are in shock have more difficulty tolerating the increased oxygen consumption that fever causes. Lowering these patients' temperatures may prevent deterioration of their condition. In addition, Mayoral et al showed that fever can worsen cerebral injury [37]. After intracerebral injury was induced on monkeys, half were maintained in a euthermic state, whereas the other half were maintained at a temperature of 40°C or more for 4 hours after the injury and were then euthanized. The hyperthermic monkey brains had a 40% increase in edema and worsening hemorrhage in the traumatized area of the brain [37]. It would therefore be prudent to maintain victims of brain–injury euthermic.

In most healthy hosts, fever has little harmful effects. There is no evidence that fever itself causes brain damage unless it reaches at least 41.7°C [27]. Fortunately, as has already been discussed, most fevers seen in children that are caused from infections rarely reach this alarming temperature. The most common side effects of fever are benign and include minimal dehydration, increased sleepiness, and discomfort. Febrile seizures only occur in 4% of febrile patients and most are self-limited without any long-term sequelae.

Pharmacologic Treatment

There is great variability in antipyretic preferences among practitioners. In general, acetaminophen and ibuprofen are the most common antipyretics used for children older than 6 months. Ibuprofen is contraindicated in children younger than 6 months, and acetylsalicylic acid is not used in infants and children due to its association with Reye syndrome. A survey of 160 pediatricians reported antipyretic preferences for acetaminophen 10 mg/kg every 4 hours, acetaminophen 15 mg/kg every 4 hours, ibuprofen 10 mg/kg every 6 hours, and ibuprofen 7.5 mg/kg every 6 hours, as 33%, 33%, 22%, and 8% respectively [38].

A meta-analysis comparing single dose ibuprofen 5 to 10 mg/kg vs acetaminophen 10 to 15 mg/kg concluded that 15% more children were likely to have a febrile temperature reduction at 4 to 6 hours after therapy with ibuprofen compared to acetaminophen. Restricting their

analysis to 10 mg/kg ibuprofen vs 10 to 15 mg/kg acetaminophen increased the antipyretic advantage of ibuprofen to 38% [39]. They did not, however, compare acetaminophen 15 mg/kg with ibuprofen 10 mg/kg dosing. The safety profiles of the medications were analogous. Another meta-analysis confirmed that ibuprofen was significantly more effective than acetaminophen in reducing fever after a single dose; however, both medications were equally efficacious when multiple doses were administered [40]. It appears that ibuprofen is somewhat more effective than acetaminophen at reducing fever and has a longer duration of action than acetaminophen after one dose. However, the drugs are similarly effective antipyretics when multiple doses are administered. Because crossover studies have not been performed, it is not known if patients who fail to respond to one medication will respond better to the other.

Fifty percent of pediatricians recommended alternating acetaminophen and ibuprofen [38]. Their method of dosing varied from acetaminophen every 4 hours alternating with ibuprofen every 6 hours to alternating the 2 products every 2 to 4 hours. Twenty-nine percent of respondents cited the American Academy of Pediatrics as the source for their regimen, although no such guidelines exist. The efficacy of alternating acetaminophen and ibuprofen has not been clearly proven. Although a few studies have analyzed single administration of alternating acetaminophen with ibuprofen by health care providers [41,42], only one study has addressed the parental administration of alternating antipyretics beyond a single dose [43].

Sarrell et al [43] randomized patients to receive either 12.5 mg/kg acetaminophen every 6 hours, ibuprofen 5 mg/kg every 8 hours, or alternating doses of acetaminophen and ibuprofen every 4 hours for 3 days. Half of the patients in each of the treatment groups were initially loaded with acetaminophen 25 mg/kg, whereas the other half were loaded with ibuprofen 10 mg/kg. The patients in the group that alternated acetaminophen with ibuprofen had significantly lower mean temperatures, received less total antipyretic medication, and reported less stress levels than either of the 2 monotherapy groups, regardless of initial loading medication. Critics of this article argue that it is not standard of care to give loading doses of antipyretic in the United States and that the antipyretic dosing was subtherapeutic. Furthermore, the alternating group used fewer doses as early as the first 24 hours, which could be due to a more self-limited cause for fever in that group [44]. The study ensured numerous safeguards including written directions, pharmacist reiteration of directions, and follow-up, which would not occur in practical clinical or telephone-care settings [45]. Concern regarding untoward consequences of medication alternation warrant validation of this study's results. In the meantime, pediatricians should be cautious and concrete about their recommendations to families.

Nonpharmacologic Treatment

Sponging reduces fever by the 3 modalities of conduction, convection, and evaporation. Through conduction, heat is exchanged from the warm body of the patient to the water. Heat moves from warm to cool air by convection. Finally, heat is lost as water evaporates from the patient's body. Several small studies have evaluated the clinical utility of sponging for fever reduction in pediatric patients with infection related fevers. Unfortunately, most of the studies have methodological limitations, making it difficult to draw definitive conclusions.

Steele et al found that sponging with ice water (4.4°C-10°C) or tepid water (29.4°C-32.2°C) after administration of acetaminophen significantly reduced fever faster than acetaminophen alone [46]. However, patients sponged with ice water had high levels of shivering and discomfort. Patients in this study were sponged until temperatures dropped below 38.3°C, which took up to 2 hours. It is impractical for families or physicians to sponge patients for this length of time. Also, temperatures were not measured after sponging was ceased to determine if there was a rebound increase in temperature. Newman compared tepid sponging after administration of antipyretic with administration of antipyretic alone [47]. He found no difference in temperature reduction between the 2 groups. However, some of the patients had received unknown dosages of antipyretics at home and patients who experienced shivering were withdrawn from the study. Sharber [48] found no significant decrease in fever among 10 febrile patients who received acetaminophen compared with 10 febrile patients who received 15 minutes of tepid sponging after receiving acetaminophen. The sample size in this study was very small.

In summary, sponging with ice water causes significant patient discomfort and should not be used. Also, sponging with alcohol in children is dangerous because the alcohol can be absorbed through the skin and cause toxicity. Antipyretic medication alone is superior to sponging alone for fever reduction. Sponging with tepid water after administration of antipyretic medication might initially drop temperature faster than medication alone, but the end result over time of this combination has not been proven to be definitively superior to medication alone.

Hyperthermia

Hyperthermia occurs when temperatures rise to alarmingly dangerous levels and is caused by mechanisms that do not involve the thermoregulatory set point. Hyperthermia supervenes when either heat production exceeds heat loss, as is the case with malignant hyperthermia, hyperthyroidism, and elevated environmental temperatures, or when heat loss is defective, as with dehydration, ectodermal dysplasia, heat stroke, or anticholinergic poisoning. During hyperthermia peripheral mechanisms

such as sweating and vasodilation fail to dissipate enough heat to decrease body temperature back to the untouched set point. Unlike fever, hyperthermia can cause confusion, delirium, stupor, or coma via an interplay of hypoxia, metabolic derangements, hypotension, and dehydration [49]. Not many patients have survived more than a few days or weeks with temperatures greater than 41.7°C [27].

Because hyperthermia does not involve the thermoregulatory center, treatment with centrally acting antipyretic medications is futile. Instead, appropriate management begins by identifying and addressing the inciting cause. Vigorous cooling techniques including removing clothing, bedside fans, cooling blankets, and sponging should be instituted. True hyperthermic emergencies should be treated with more drastic measures including immersion in ice water, intravenous administration of cool fluids, intraperitoneal and gastric lavage with cool fluids, and even extracorporeal circulation [49].

Summary

Fever phobia causes both health care providers and parents to overtreat fevers. This places children at risk of medication toxicity, needless repeat temperature readings, and parental panic. Fortunately, the homeostatic balance of the body's temperature control mechanism prevents fevers from reaching alarming levels of hyperthermia for most healthy individuals. It is the physician's role to educate parents regarding the facts and myths about fevers to decrease unsubstantiated parental fears.

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