Chapter 18: Fever

Neeraj K. Surana; Charles A. Dinarello; Reuven Porat

INTRODUCTION

Body temperature is controlled by the hypothalamus. Neurons in both the preoptic anterior hypothalamus and the posterior hypothalamus receive two kinds of signals: one from peripheral nerves that transmit information from warmth/cold receptors in the skin and the other from the temperature of the blood bathing the region. These two types of signals are integrated by the thermoregulatory center of the hypothalamus to maintain normal temperature. In a neutral temperature environment, the human metabolic rate produces more heat than is necessary to maintain the core body temperature in the range of 36.5–37.5°C (97.7–99.5°F).

A normal body temperature is ordinarily maintained despite environmental variations because the hypothalamic thermoregulatory center balances the excess heat production derived from metabolic activity in muscle and the liver with heat dissipation from the skin and lungs. According to a study of >35,000 individuals ≥18 years of age seen in routine medical visits, the mean oral temperature is 36.6°C (95% confidence interval, 35.7–37.3°C). In light of this study, *a temperature of >37.7°C (>99.9°F), which represents the 99th percentile for healthy individuals, defines a fever.* Importantly, higher ambient temperatures are linked to higher baseline body temperatures. Additionally, body temperatures have diurnal and seasonal variation, with low levels at 8 A.M. and during summer and higher levels at 4 P.M. and during winter. Baseline temperatures are also affected by age (lower by 0.02°C for every 10-year increase in age), demographics (African-American women have temperatures 0.052°C higher than white men), and comorbid conditions (cancer is associated with 0.02°C higher temperatures; hypothyroidism is linked to temperatures lower by 0.01°C). After controlling for age, sex, race, vital signs, and comorbidities, an increase in baseline temperature of 0.15°C (or 1 standard deviation) intriguingly translates into a 0.52% absolute increase in 1-year mortality.

Rectal temperatures are generally 0.4°C (0.7°F) higher than oral readings. The lower oral readings are probably attributable to mouth breathing, which is a factor in patients with respiratory infections and rapid breathing. Lower-esophageal temperatures closely reflect core temperature. Tympanic membrane thermometers measure radiant heat from the tympanic membrane and nearby ear canal and display that absolute value (*unadjusted mode*) or a value automatically calculated from the absolute reading on the basis of nomograms relating the radiant temperature measured to actual core temperatures obtained in clinical studies (*adjusted mode*). These measurements, although convenient, may be more variable than directly determined oral or rectal values. Studies in adults show that readings are lower with unadjusted-mode than with adjusted-mode tympanic membrane thermometers and that unadjusted-mode tympanic membrane values are 0.8°C (1.6°F) lower than rectal temperatures.

In women who menstruate, the A.M. temperature is generally lower during the 2 weeks before ovulation; it then rises by ~0.6°C (1°F) with ovulation and stays at that level until menses occur. During the luteal phase, the amplitude of the circadian rhythm remains the same.

FEVER VERSUS HYPERTHERMIA

Fever is an elevation of body temperature that exceeds the normal daily variation and occurs *in conjunction with an increase in the hypothalamic set point* (e.g., from 37°C to 39°C). This shift of the set point from “normothermic” to febrile levels very much resembles the resetting of the home thermostat to a higher level in order to raise the ambient temperature in a room. Once the hypothalamic set point is raised, neurons in the vasomotor center are activated and vasoconstriction commences. The individual first notices vasoconstriction in the hands and feet. Shunting of blood away from the periphery to the internal organs essentially decreases heat loss from the skin, and the person feels cold. For most fevers, body temperature increases by 1–2°C. Shivering, which increases heat production from the muscles, may begin at this time; however, shivering is not required if mechanisms of heat conservation raise blood temperature sufficiently. Nonshivering heat production from the liver also contributes to increasing core temperature. Behavioral adjustments (e.g., putting on more clothing or bedding) help raise body temperature by decreasing heat loss.

The processes of heat conservation (vasoconstriction) and heat production (shivering and increased nonshivering thermogenesis) continue until the temperature of the blood bathing the hypothalamic neurons matches the new "thermostat setting." Once that point is reached, the hypothalamus maintains the temperature at the febrile level by the same mechanisms of heat balance that function in the afebrile state. When the hypothalamic set point is again reset downward (in response to either a reduction in the concentration of pyrogens or the use of antipyretics), the processes of heat loss through vasodilation and sweating are initiated. Loss of heat by sweating and vasodilation continues until the blood temperature at the hypothalamic level matches the lower setting. Behavioral changes (e.g., removal of clothing) facilitate heat loss.

A fever of >41.5°C (>106.7°F) is called *hyperpyrexia*. This extraordinarily high fever can develop in patients with severe infections but most commonly occurs in patients with central nervous system (CNS) hemorrhages. In the preantibiotic era, fever due to a variety of infectious diseases rarely exceeded 106°F, and there has been speculation that this natural "thermal ceiling" is mediated by neuropeptides functioning as central antipyretics.

In rare cases, the hypothalamic set point is elevated as a result of local trauma, hemorrhage, tumor, or intrinsic hypothalamic malfunction. The term *hypothalamic fever* is sometimes used to describe elevated temperature caused by abnormal hypothalamic function. However, most patients with hypothalamic damage have *sub*normal, not *supra*normal, body temperatures.

Although most patients with elevated body temperature have fever, there are circumstances in which elevated temperature represents not fever but *hyperthermia* (*heat stroke*). Hyperthermia is characterized by an uncontrolled increase in body temperature that exceeds the body's ability to lose heat. The setting of the hypothalamic thermoregulatory center is unchanged. In contrast to fever in infections, hyperthermia does not involve pyrogenic molecules. Exogenous heat exposure and endogenous heat production are two mechanisms by which hyperthermia can result in dangerously high internal temperatures. Excessive heat production can easily cause hyperthermia despite physiologic and behavioral control of body temperature. For example, work or exercise in hot environments can produce heat faster than peripheral mechanisms can lose it. **For a detailed discussion of hyperthermia, see Chap. 465.**

It is important to distinguish between fever and hyperthermia since hyperthermia can be rapidly fatal and characteristically does not respond to antipyretics. In an emergency situation, however, making this distinction can be difficult. For example, in systemic sepsis, fever (hyperpyrexia) can be rapid in onset, and temperatures can exceed 40.5°C (104.9°F). Hyperthermia is often diagnosed on the basis of the events immediately preceding the elevation of core temperature—e.g., heat exposure or treatment with drugs that interfere with thermoregulation. In patients with heat stroke syndromes and in those taking drugs that block sweating, the skin is hot but dry, whereas in fever, the skin can be cold as a consequence of vasoconstriction. Antipyretics do not reduce the elevated temperature in hyperthermia, whereas in fever—and even in hyperpyrexia—adequate doses of either aspirin or acetaminophen usually result in some decrease in body temperature.

PATHOGENESIS OF FEVER

PYROGENS

The term *pyrogen* (Greek *pyro*, "fire") is used to describe any substance that causes fever. *Exogenous* pyrogens are derived from outside the patient; most are microbial products, microbial toxins, or whole microorganisms (including viruses). The classic example of an exogenous pyrogen is the lipopolysaccharide (endotoxin) produced by all gram-negative bacteria. Pyrogenic products of gram-positive organisms include the enterotoxins of *Staphylococcus aureus* and the groups A and B streptococcal toxins, also called *superantigens*. One staphylococcal toxin of clinical importance is that associated with isolates of *S. aureus* from patients with toxic shock syndrome. These products of staphylococci and streptococci cause fever in experimental animals when injected intravenously at concentrations of 1–10 μg/kg. Endotoxin is a highly pyrogenic molecule in humans: when injected intravenously into volunteers, a dose of 2–3 ng/kg produces fever, leukocytosis, acute-phase proteins, and generalized symptoms of malaise.

PYROGENIC CYTOKINES

Cytokines are small proteins (molecular mass, 10,000–20,000 Da) that regulate immune, inflammatory, and hematopoietic processes. For example, the elevated leukocytosis seen in several infections with an absolute neutrophilia is attributable to the cytokines interleukin (IL) 1 and IL-6. Some cytokines also cause fever; formerly referred to as *endogenous pyrogens*, they are now called *pyrogenic cytokines*. The pyrogenic cytokines include IL-1, IL-6, tumor necrosis factor (TNF), and ciliary neurotropic factor, a member of the IL-6 family. Fever is a prominent side effect of interferon α therapy. Each pyrogenic cytokine is encoded by a separate gene, and each has been shown to cause fever in laboratory animals and in humans. When injected into humans at low doses (10–100 ng/kg), IL-1 and TNF produce fever; in contrast, for IL-6, a dose of 1–10 μg/kg is required for fever production.

A wide spectrum of bacterial and fungal products induce the synthesis and release of pyrogenic cytokines. However, fever can be a manifestation of disease in the absence of microbial infection. For example, inflammatory processes such as pericarditis, trauma, stroke, and routine immunizations induce the production of IL-1, TNF, and/or IL-6; individually or in combination, these cytokines trigger the hypothalamus to raise the set point to febrile levels.

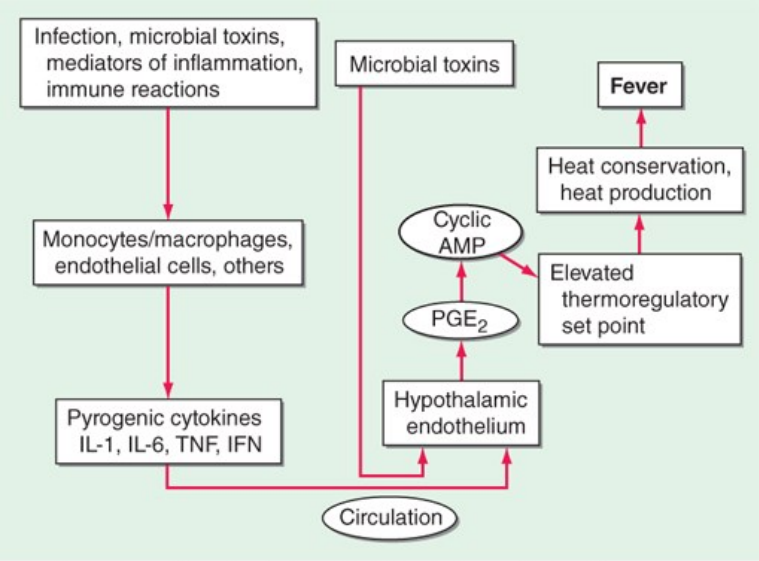
ELEVATION OF THE HYPOTHALAMIC SET POINT BY CYTOKINES

During fever, levels of prostaglandin E_2 (PGE_2) are elevated in hypothalamic tissue and the third cerebral ventricle. The concentrations of PGE_2 are highest near the circumventricular vascular organs (organum vasculosum of lamina terminalis)—networks of enlarged capillaries surrounding the hypothalamic regulatory centers. Destruction of these organs reduces the ability of pyrogens to produce fever. Most studies in animals have failed to show, however, that pyrogenic cytokines pass from the circulation into the brain itself. Thus, it appears that both exogenous pyrogens and pyrogenic cytokines interact with the endothelium of these capillaries and that this interaction is the first step in initiating fever—i.e., in raising the set point to febrile levels.

The key events in the production of fever are illustrated in **Fig. 18-1**. Myeloid and endothelial cells are the primary cell types that produce pyrogenic cytokines. Pyrogenic cytokines such as IL-1, IL-6, and TNF are released from these cells and enter the systemic circulation. Although these circulating cytokines lead to fever by inducing the synthesis of PGE_2, they also induce PGE_2 in peripheral tissues. The increase in PGE_2 in the periphery accounts for the nonspecific myalgias and arthralgias that often accompany fever. It is thought that some systemic PGE_2 escapes destruction by the lung and gains access to the hypothalamus via the internal carotid. However, it is the elevation of PGE_2 in the brain that starts the process of raising the hypothalamic set point for core temperature.

FIGURE 18-1

Chronology of events required for the induction of fever. AMP, adenosine 5′-monophosphate; IFN, interferon; IL, interleukin; PGE_2, prostaglandin E_2; TNF, tumor necrosis factor.



There are four receptors for PGE_2, and each signals the cell in different ways. Of the four receptors, the third (EP-3) is essential for fever: when the gene for this receptor is deleted in mice, no fever follows the injection of IL-1 or endotoxin. Deletion of the other PGE_2 receptor genes leaves the fever mechanism intact. Although PGE_2 is essential for fever, it is not a neurotransmitter. Rather, the release of PGE_2 from the brain side of the hypothalamic endothelium triggers the PGE_2 receptor on glial cells, and this stimulation results in the rapid release of cyclic adenosine 5′-monophosphate (cAMP),

which is a neurotransmitter. As shown in Fig. 18-1, the release of cAMP from glial cells activates neuronal endings from the thermoregulatory center that extend into the area. The elevation of cAMP is thought to account for changes in the hypothalamic set point either directly or indirectly (by inducing the release of neurotransmitters). Distinct receptors for microbial products are located on the hypothalamic endothelium. These receptors are called *Toll-like receptors* and are similar in many ways to IL-1 receptors. IL-1 receptors and Toll-like receptors share the same signal-transducing mechanism. Thus, the direct activation of Toll-like receptors or IL-1 receptors results in PGE_2 production and fever.

PRODUCTION OF CYTOKINES IN THE CNS

Cytokines produced in the brain may account for the hyperpyrexia of CNS hemorrhage, trauma, or infection. Viral infections of the CNS induce microglial and possibly neuronal production of IL-1, TNF, and IL-6. In experimental animals, the concentration of a cytokine required to cause fever is several orders of magnitude lower with direct injection into the brain substance or brain ventricles than with systemic injection. Therefore, cytokines produced in the CNS can raise the hypothalamic set point, bypassing the circumventricular organs. CNS cytokines likely account for the hyperpyrexia of CNS hemorrhage, trauma, or infection.

APPROACH TO THE PATIENT WITH FEVER

History and Physical Examination

There are a range of disease processes that present with fever as a cardinal manifestation, and a thorough history can help distinguish between these broad categories **(Table 18-1)**. The chronology of events preceding fever, including exposure to other symptomatic individuals or to vectors of disease, should be ascertained. Electronic devices for measuring oral, tympanic membrane, or rectal temperatures are reliable, but the same site should be used consistently to monitor a febrile disease. Moreover, physicians should be aware that newborns, elderly patients, patients with chronic hepatic or renal failure, and patients taking glucocorticoids or being treated with an anticytokine may have active disease in the absence of fever because of a blunted febrile response.

TABLE 18-1

Disease Categories That Present with Fever as a Cardinal Sign

Infectious diseases
Autoimmune and noninfectious inflammatory disorders
Cancer
Medication related (e.g., vaccines, drug fever)
Endocrine disorders (e.g., hyperthyroidism)
Intrinsic hypothalamic malfunction

Laboratory Tests

The workup should include a complete blood count; a differential count should be performed manually or with an instrument sensitive to the identification of juvenile or band forms, toxic granulations, and Döhle bodies, which are suggestive of bacterial infection. Neutropenia may be present with some viral infections.

Measurement of circulating cytokines in patients with fever is not helpful since levels of cytokines such as IL-1 and TNF in the circulation often are below the detection limit of the assay or do not coincide with fever. However, in patients with low-grade fevers or with suspected occult disease, the most valuable measurements are the C-reactive protein (CRP) level and the erythrocyte sedimentation rate. These markers of inflammatory processes

are particularly helpful in detecting occult disease. Measurement of circulating IL-6, which induces CRP, can be useful. However, whereas IL-6 levels may vary during a febrile disease, CRP levels remain elevated. **Acute-phase reactants are discussed in Chap. 304.**

Fever in Patients Receiving Anticytokine Therapy

Patients receiving long-term treatment with anticytokine-based regimens are at increased risk of infection because of lowered host defenses. For example, latent *Mycobacterium tuberculosis* infection can disseminate in patients receiving anti-TNF therapy. With the increasing use of anticytokines to reduce the activity of IL-1, IL-6, IL-12, IL-17, or TNF in patients with Crohn's disease, rheumatoid arthritis, or psoriasis, the possibility that these therapies blunt the febrile response should be kept in mind.

The blocking of cytokine activity has the distinct clinical drawback of lowering the level of host defenses against both routine bacterial and opportunistic infections such as *M. tuberculosis* and fungal infections. The use of monoclonal antibodies to reduce IL-17 in psoriasis increases the risk of systemic candidiasis.

In nearly all reported cases of infection associated with anticytokine therapy, fever is among the presenting signs. However, the extent to which the febrile response is blunted in these patients remains unknown. Therefore, low-grade fever in patients receiving anticytokine therapies is of considerable concern. The physician should conduct an early and rigorous diagnostic evaluation in these cases. The febrile response is also blunted in patients receiving chronic glucocorticoid therapy or anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs).

TREATMENT OF FEVER

The Decision to Treat Fever

In deciding whether to treat fever, it is important to remember that fever itself is not an illness: it is an ordinary response to a perturbation of normal host physiology. Most fevers are associated with self-limited infections, such as common viral diseases. The use of antipyretics is not contraindicated in these infections: no significant clinical evidence indicates either that antipyretics delay the resolution of viral or bacterial infections or that fever facilitates recovery from infection or acts as an adjuvant to the immune system. In short, treatment of fever and its symptoms with routine antipyretics does no harm and does not slow the resolution of common viral and bacterial infections.

However, in bacterial infections, the withholding of antipyretic therapy can be helpful in evaluating the effectiveness of a particular antibiotic, especially in the absence of positive cultures of the infecting organism, and the routine use of antipyretics can mask an inadequately treated bacterial infection. Withholding antipyretics in some cases may facilitate the diagnosis of an unusual febrile disease. Temperature–pulse dissociation (*relative bradycardia*) occurs in typhoid fever, brucellosis, leptospirosis, some drug-induced fevers, and factitious fever. As stated earlier, in newborns, elderly patients, patients with chronic liver or kidney failure, and patients taking glucocorticoids, fever may not be present despite infection. Hypothermia can develop in patients with septic shock.

Some infections have characteristic patterns in which febrile episodes are separated by intervals of normal temperature. For example, *Plasmodium vivax* causes fever every third day, whereas fever occurs every fourth day with *Plasmodium malariae*. Another relapsing fever is related to *Borrelia* infection, with days of fever followed by a several-day afebrile period and then a relapse into additional days of fever. In the Pel-Ebstein pattern, fever lasting 3–10 days is followed by afebrile periods of 3–10 days; this pattern can be classic for Hodgkin's disease and other lymphomas. In cyclic neutropenia, fevers occur every 21 days and accompany the neutropenia. There are also a number of periodic fever syndromes (e.g., familial Mediterranean fever, TNF receptor–associated periodic syndrome [TRAPS]) that differ in their periodicity, duration of attack, constellation of clinical features, genetic causes, and therapies **(Chap. 369)**. Understanding these clinical differences can help tailor diagnostic testing to confirm the diagnosis and guide therapy.

Anticytokine Therapy to Reduce Fever in Autoimmune and Autoinflammatory Diseases

Recurrent fever is documented at some point in most autoimmune diseases and many autoinflammatory diseases, which include the periodic fever syndromes as well as disorders of inflammasomes (e.g., NLRP3, pyrin) and other components of the innate immune system **(Chap. 349)**. Although fever can be a manifestation of autoimmune diseases, recurrent fevers are characteristic of autoinflammatory diseases, including uncommon diseases such as adult and juvenile Still's disease, familial Mediterranean fever, and hyper-IgD syndrome but also common diseases such as idiopathic pericarditis and gout. In addition to recurrent fevers, neutrophilia and serosal inflammation characterize autoinflammatory diseases. The fevers

associated with many of these illnesses are dramatically reduced by blocking of IL-1 activity with anakinra or canakinumab. Anticytokines therefore reduce fever in autoimmune and autoinflammatory diseases. Although fevers in autoinflammatory diseases are mediated by IL-1β, patients also respond to antipyretics.

Mechanisms of Antipyretic Agents

The reduction of fever by lowering of the elevated hypothalamic set point is a direct function of reduction of the PGE_2 level in the thermoregulatory center. The synthesis of PGE_2 depends on the constitutively expressed enzyme cyclooxygenase. The substrate for cyclooxygenase is arachidonic acid released from the cell membrane, and this release is the rate-limiting step in the synthesis of PGE_2. Therefore, inhibitors of cyclooxygenase are potent antipyretics. The antipyretic potency of various drugs is directly correlated with the inhibition of brain cyclooxygenase. Acetaminophen is a poor cyclooxygenase inhibitor in peripheral tissue and lacks noteworthy anti-inflammatory activity; in the brain, however, acetaminophen is oxidized by the P450 cytochrome system, and the oxidized form inhibits cyclooxygenase activity. Moreover, in the brain, the inhibition of another enzyme, COX-3, by acetaminophen may account for the antipyretic effect of this agent. However, COX-3 is not found outside the CNS.

Oral aspirin and acetaminophen are equally effective in reducing fever in humans. NSAIDs such as ibuprofen and specific inhibitors of COX-2 also are excellent antipyretics. Chronic, high-dose therapy with antipyretics such as aspirin or any NSAID does not reduce normal core body temperature. Thus, PGE_2 appears to play no role in normal thermoregulation.

As effective antipyretics, glucocorticoids act at two levels. First, similar to the cyclooxygenase inhibitors, glucocorticoids reduce PGE_2 synthesis by inhibiting the activity of phospholipase A_2, which is needed to release arachidonic acid from the cell membrane. Second, glucocorticoids block the transcription of the mRNA for the pyrogenic cytokines. Limited experimental evidence indicates that ibuprofen and COX-2 inhibitors reduce IL-1-induced IL-6 production and may contribute to the antipyretic activity of NSAIDs.

Regimens for The Treatment of Fever

The objectives in treating fever are first to reduce the elevated hypothalamic set point and second to facilitate heat loss. Reducing fever with antipyretics also reduces systemic symptoms of headache, myalgias, and arthralgias.

Oral aspirin and NSAIDs effectively reduce fever but can adversely affect platelets and the gastrointestinal tract. Therefore, acetaminophen is preferred as an antipyretic. In children, acetaminophen or oral ibuprofen must be used because aspirin increases the risk of Reye's syndrome. If the patient cannot take oral antipyretics, parenteral preparations of NSAIDs and rectal suppositories of various antipyretics can be used.

Treatment of fever in some patients is highly recommended. Fever increases the demand for oxygen (i.e., for every increase of 1°C over 37°C, there is a 13% increase in oxygen consumption) and can aggravate the condition of patients with preexisting impairment of cardiac, pulmonary, or CNS function. Children with a history of febrile or nonfebrile seizure should be aggressively treated to reduce fever. However, it is unclear what triggers the febrile seizure, and there is no correlation between absolute temperature elevation and onset of a febrile seizure in susceptible children.

In hyperpyrexia, the use of cooling blankets facilitates the reduction of temperature; however, cooling blankets should not be used without oral antipyretics. In hyperpyretic patients with CNS disease or trauma (CNS bleeding), reducing core temperature mitigates the detrimental effects of high temperature on the brain.

For a discussion of treatment for hyperthermia, see Chap. 465.

FURTHER READING

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