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Fever and Febrile Syndromes

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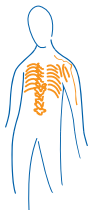

INTRODUCTION

Fever is one of the most common problems requiring medical evaluation. Fever is an elevation in core body temperature greater than normal daily variation, which is 36.8° C ± 0.4° C (98.2° F ± 0.7° F). Documentation of true fever can be important evidence of infectious processes that warrant investigation. Although fever is characteristic of most infections, it also occurs in noninfectious conditions such as autoimmune and inflammatory diseases, malignancy, and trauma.

This chapter reviews the pathogenesis of the febrile response, the approach to the acutely ill patient with fever, and fever of unknown origin. Fever can be associated with infections, such as those from animal exposures, or with common clinical scenarios in which it may occur as the sole complaint, manifest with rash, or develop with lymphadenopathy. A word of caution about the difference between true and factitious fever is offered at the end of the chapter.

PATHOGENESIS

Thermoregulation of core body temperature is one of the most important mechanisms in mammalian and human physiology. The hypothalamic heat-regulating set point shifts in response to infection or inflammation mediated primarily by the host's monocytes and macrophages, which are activated as they encounter exogenous bacterial substances, toxins, or the cellular products of trauma.

Monocytes and macrophages produce small proteins called *cytokines,* such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF). They are collectively known as *endogenous pyrogens* because they actively increase body temperature by increasing the hypothalamic set point, which is the normal temperature for the body that is controlled by the hypothalamus. IL-1 and other endogenous pyrogens are released by macrophages at the site of infection and travel through the bloodstream to the hypothalamus, where they elevate levels of prostaglandin E_2 (PGE_2). Elevated PGE_2 levels increase the set point, and thermoregulatory mechanisms raise the body's core temperature. IL-1 also induces production of PGE_2 in peripheral tissues, which causes the nonspecific myalgias and arthralgias that often accompany fever. Prostaglandin inhibitors such as aspirin or acetaminophen block prostaglandin synthesis and reduce elevated temperatures.

Thermoregulatory control is initiated through sensory neurons in the skin, abdomen, and spinal cord. Central nervous system (CNS) thermoreceptors sense and integrate temperature information. After the hypothalamic set point is raised, the firing rates of neurons in the vasomotor center are altered, causing peripheral vasoconstriction and producing a noticeable cold sensation in the hands and feet. Blood is shunted away from the periphery to the internal organs, and this process is sufficient to raise core body temperature by 1° to 2° C.

Other signaling mechanisms have roles in thermoregulation. The adipocyte-derived hormone leptin actively controls energy homeostasis, and thermogenesis in fat tissue contributes to increasing core temperature. Thermogenesis is important in fighting infection and in responding to cold-induced heat production. Fever has direct antimicrobial effects in some infections such as neurosyphilis and salmonellosis, and elevated temperature augments humoral and cellular immune responses. IL-1 acts independently on two physiologic systems: thermoregulation and iron metabolism. IL-1 can stimulate a wide range of host defenses to conduct a synergistic response to infection.

Fever also can have deleterious effects. It may lead to disorientation and confusion in persons with underlying brain disease and in healthy older individuals. Tachycardia can increase cardiopulmonary work, precipitating congestive heart failure or myocardial infarction in persons with significant cardiopulmonary disease. Fever should be controlled with antipyretics for comfort and to avoid compromising individuals with multiple medical problems. Acetaminophen is preferred for control of fever in children because of the risk of Reye's syndrome with salicylate use.

The terms *fever*, *hyperthermia*, and *hyperpyrexia* are not synonymous. Although most patients with elevated temperature have fever (>38.3° C or 100.9° F), some conditions can increase the body temperature by overriding or bypassing the normal homeostatic mechanism and may even produce body temperatures in excess of 41° C or 105.8° F (i.e., hyperthermia), which can be rapidly fatal and does not respond to antipyretics. Rapid cooling is critical to the patient's survival in hyperthermic conditions such as heat stroke. Even in otherwise healthy individuals, heat stroke can occur after vigorous exercise and prolonged exposure to high environmental temperatures and humidity. Heat stroke is marked by temperatures greater than 40.6° C (105.1° F), altered sensorium or coma, and cessation of sweating. Treatment includes covering the patient with wet compresses followed by intravenous infusion of fluids appropriate to correct fluid and electrolyte losses.

Severe hyperthermia may be a heritable reaction to anesthetics (i.e., malignant hyperthermia) or a response to phenothiazines (i.e., neuroleptic malignant syndrome). Serotonin syndrome, which often includes fever, is classically associated with the simultaneous administration of two serotonergic agents. It can also occur after initiation of a single serotonergic drug that increases the serotonin level of individuals who are particularly sensitive to