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A Clinical Overview Understanding of Fever Pathophysiology, Diagnosis and Treatment

Sireesha Vankodoth [1,*], Lakshmi Prasanna Dakoji [1], Shubham kumar Kashyap [1], Lakshmi priya Vadlapudi [1] and Rama Rao. T [2]

[1] *Department of pharm D, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India.*
[2] *Department of pharmaceutical sciences, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India.*

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Abstract

Since ancient times, fever has been a common symptom of illness. Fever is a complex physiological response mediated by cytokine-induced hypothalamic prostaglandin production, serving as a defence mechanism against infections. The central nervous system uses endocrine, neurological, immunological and behavioral systems to control the fever response. In addition to a controlled increase in body temperature, fever frequently manifests as a variety of illness-related behaviors, modifications to the physiological and metabolic properties of bodily systems, and adjustments to immunological responses. Therefore, fever and the febrile response continue to play important roles in the etiology, clinical manifestation, and prognosis of several illnesses and disorders. A process known as a fever or pyrexia occurs when the body's normal temperature rises above equilibrium. Accurate diagnosis involves a thorough history, physical examination, and targeted investigations. Treatment focuses on managing the underlying cause and providing symptomatic relief, with antipyretics playing a key role in patient comfort.

Keywords: Cytokine-Induced; Infection; Hyperthermia; Pyrexia

1. Introduction

Fever, also known as pyrexia, is a regulated elevation of body temperature above the normal range, typically above 38°C (100.4°F). It is a common clinical manifestation of various underlying conditions, primarily infectious and inflammatory processes which is a common physiological reaction to infection or inflammation. Pyrogens cause the hypothalamus to boost the body's set-point temperature, in result of the immune system's reaction. A comprehension of its mechanism facilitates diagnosis and treatment. To determine the underlying causes, diagnosis entails both laboratory testing and clinical evaluation. [1] The pathogenesis, clinical manifestation and outcome of numerous illnesses and diseases are still significantly influenced by the febrile response. Thus, diagnosing, treating, and monitoring a variety of conditions and diseases all depend on an understanding of fever and febrile response. The pathophysiology of the fever response and explains the various forms and patterns of fever, along with their clinical implications. The different medical conditions referred to as "fever". Normal physiological processes in the human body, such as metabolic shifts, sleep/wake cycles, hormone variability, and fluctuating activity levels are the cause of this variance in core body temperature. [2] The thermoregulatory system is required to control body temperature. The preoptic region of the anterior hypothalamus is the primary thermoregulatory center in the central nervous system thought to be where peripheral and centrally generated temperature signals are received and combined.[3] The mean oral temperature was 36.8±0.4 °C (98.2 °F). For healthy middle-aged adults, fever can be defined as an oral temperature of >37.2◦ C (>99◦ F) in the morning or a temperature of >37.7◦ C (>100◦ F) at any time of day. [4]

* Corresponding author: Vankodoth Sireesha.

1.1. Symptoms of Fever

A series of clinical and behavioral signs that define the febrile response are caused by a feedback loop that is started when humoral and neural fever signals raise the thermal balance point to a greater level. Heat loss is prevented by skin vasoconstriction (which causes goosebumps and chills) and behavioral strategies including reducing body surface area by assuming a fetal position, wearing thick clothing and seeking out warmer surroundings in order to reach the new balancing point. [5] Although a feeling of chilliness is frequent with fever of any cause and has little specificity, an acute bacterial infection like pneumococcal pneumonia is suggested by a sudden onset of fever with one or two strong chills (rigors) of teeth-chattering, bed-shaking intensity [6]

1.2. Pathophysiology

When the body's thermoregulatory set-point is raised by endogenous or exogenous pyrogens, a fever results. In hyperthermia, either endogenous heat production or external heat exposure causes the body temperature to rise uncontrollably while the set-point remains unchanged. Patients with severe illnesses may experience hyperpyrexia, which is defined as a temperature above 41 degrees Celsius. Patients with CNS hemorrhages may also experience hyperpyrexia, which is linked to a bad prognosis. Increased intracranial pressure, ischemic brain injury, worsening of cerebral edema and even death can result from elevated brain temperature. [7] The pyrogenic and anti-pyretic qualities of different exogenous and endogenous chemicals determine the start, expression, and control of the febrile reaction. Cryogens stop excessive temperature elevation, whereas pyrogens either directly or indirectly cause fever. The magnitude and duration of the febrile response to each immunological challenge are determined by the equilibrium in the interactions between pyrogens and cyrogens. [8]

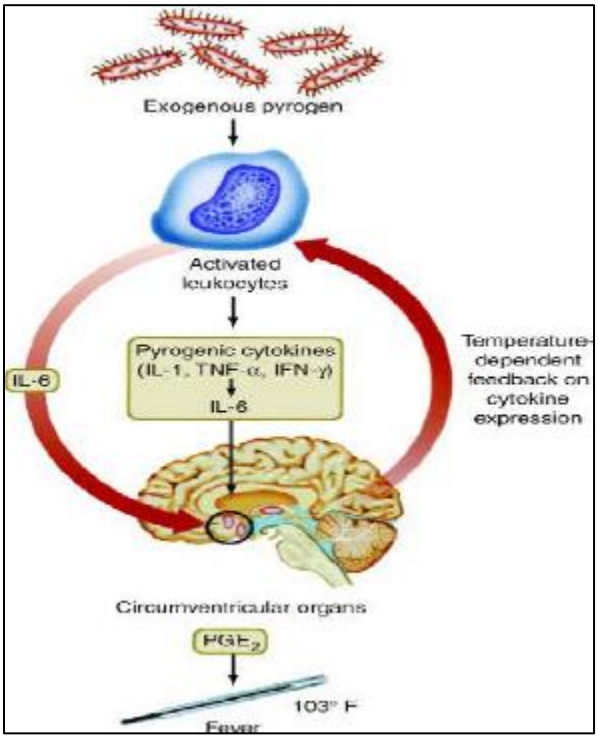

Figure 1 Pathophysiology of fever

Fever is initiated by pyrogens—substances that induce fever. These can be endogenous (produced by the body) or exogenous (originating outside the body). Exogenous Pyrogens are the Components of microorganisms such as lipopolysaccharides (LPS) from bacterial cell walls. Endogenous Pyrogens include Cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-alpha (IFN-α), produced by immune cells in response to infection or inflammation. [9]

1.3. Cytokine Release and Hypothalamic Action

These pyrogens stimulate the production of prostaglandin E2 (PGE2) in the hypothalamus, which acts on the thermoregulatory center to elevate the body's set point temperature. [10] Easily diffusing across the blood-brain

barrier, prostaglandin E2 attaches to certain PGE2 receptors (EP3 receptor) in the preoptic region and triggers thermal neurons in the anterior hypothalamus to reach a higher thermal balancing point. [11]

1.4. Adjustment of Body Temperature

The body starts heat-generating processes including shivering and vasoconstriction to achieve the new, higher set point, which raises the core temperature. The hypothalamic set point stays high when the fever is created until the pyrogens are removed. [12] The hypothalamic set point returns to normal, PGE2 levels drop, and the body releases heat as the pyrogens are eliminated, causing defervescence, or a return to normal body temperature. [13]

1.5. Types and patterns of fever

1.5.1. The humoral pathway

Fever signals in this system are conveyed by pyrogenic cytokines or by elements of microbial products known as pathogen associated molecular patterns (PAMPS). [14]

1.5.2. The neural pathway

Peripheral nerves like the vagus nerve and cutaneous sensory nerves can transmit peripheral fever signals to the central nervous system. The brain pathway's activation is thought to be another mechanism that quickly initiates fever. That localized PGE2 production at inflammatory areas triggers cold-sensitive cutaneous nerves, which send fever signals to the brain regions in charge of fever production. The vagal pathway is mediated by norepinephrine, which causes noticeable increases in core temperature.the first is alpha (1)-adrenoceptor (AR)-mediated, quick in onset, and PGE2-independent. while the second is alpha (2)-AR-mediated, delayed, and PGE2 dependent,[15]

Based on duration, fevers might be arbitrarily categorized as acute, subacute, or chronic. Acute fevers, which last less than seven days, are indicative of infectious disorders including malaria and upper respiratory tract infections caused by viruses, whereas sub-acute fevers, which typically last more than two weeks, Fever that lasts longer than two weeks is usually indicative of connective tissue illnesses, cancer, viral infections like HIV, and chronic bacterial infections like tuberculosis. Untreated acute fever might develop into a chronic or persistent condition. The temperature of the body can also be divided into four categories:

Low (100.5-102.2^{o}F), moderate (102.2-104.0 ^{o}F), high (104.1-106.0 ^{o}F), and hyperpyrexia (>106.0 ^{o}F). [16]

Drug fevers

caused by antibiotics or other drugs show up as temperature increases from 100°F to over 106°F. The majority of medication fever between 102°F and 104°F. The "relatively good" appearance of the patient is a clinical indicator of medication fever. Caused by a number of medications, but usually Procainamide, antibiotics with beta-lactams the triazolidin. [17]

Dengue fever

Often known as break bone fever. Caused by four kinds of dengue virus (DENV-1), (DENV-2), (DENV-3), (DENV-4) any one of the viruses can infect a mosquito and cause dengue fever. Symptoms include skin rash, headache, nausea, joint and muscular pain, and fever.duration 3–14 days following infection and last for up to 10 days [18]

Rlasping fever

caused by certain bacteria in the genus Borelli, transmitted through the bites of lice or soft-bodied ticks. It is characterised by sudden fever, chills and joint pain.The: Fever lasts 2-9 days and then recurs. During seven to ten days, doxycycline 100 mg twice a day is used to treat relapsing fever. [19]

Malaria fever

caused by a plasmodium parasite of malaria. Humans contract the parasite when bitten by an infected mosquito, fever might reoccur every 48 or 72 hours and last up to 10 hours at a time.it is diagnoised by a blood test, such as a rapid diagnostic test (RDT) or blood smear. Age-specific ACT-AL for three days + 14 days of 0.25 mg/kg of body weight of primaquine each day. [20]

Typhoid fever

a prevalent disease that is spread throughout the world by consuming food or water tainted with an infected person's excrement that contains the Salmonella typhi bacteria. sympyoms like Extended high fever, exhaustion, headache, and nausea, pain in the abdomen, and diarrhoea or constipation. diagnoised by Specimens of stool, blood, or urine, Platelet count, ELISA blood test, fluorescence antibody study, blood culture, bone marrow culture. Duration about 3-5 weeks when treated, but if left untreated, it can potentially be fatal or linger for months. Fluor quinolones and antibiotics are used to treat typhoid fever. Macrolides, Cephalosporins. Carbapenems. [21]

Urinary Tarct infection fever

it is a Bacterial infection that can affect the bladder, urethra, ureters, or kidneys. caused by Mainly Escherichia coli, or E. coli, bacteria.symptoms like shivers, trembling, or sweats at night, weariness and an overall bad mood, higher than 101°F (38.3°C) fever, discomfort in the back, side, or groin, Reddened, flushed, or heated skin. Duration few days. diagnoised by urine culture and analysis. Medicines known as sulfonamides, or sulphas, like trimethoxazole/sulfamethoxazole. Amoxicillin. [22]

Pneumonia

it is an infection that irritates one or both of the lungs' air sacs is called pneumonia. Cause of viral pneumonia in adults are the flu (influenza virus) and the common cold (rhinovirus). Symptoms like Coughing up mucus that can turn green, yellow, or even crimson Sweating, chills, and a fever breathing difficulty. Duration is one to two weeks with treatment. Diagnosis by chest x-ray, pulse oximetry. Treatment is to consume over-the-counter drugs such as acetaminophen, aspirin, ibuprofen, and naproxen. [23]

2. Diagnosis

A diagnostics approach to fever or hyperthermia includes:

- Duration, pattern (intermittent, remittent, sustained, relapsing).
- Associated symptoms (rash, cough, dysuria, abdominal pain).
- Recent travel, exposures, vaccination history.
- Immunization status and co morbidities.

2.1. Laboratory Investigations:

- Complete Blood Count (CBC): Leukocytosis or leukopenia
- Blood cultures: To identify bacteremia
- Urinalysis and Urine Culture: For urinary tract infections
- Serology and PCR: For viral or specific infectious agents
- Imaging: Chest X-ray, ultrasound, or CT scans if localized signs suggest specific pathology.
- Additional Tests: In persistent or unexplained fevers, consider more specialized tests like tuberculosis testing, autoimmune panels, or bone marrow biopsy.[24]

3. Treatment

Antipyretics, which lower PGE2 levels in the hypothalamus by blocking the cyclooxygenase (COX) enzyme, are commonly used to treat fevers. Additional antipyretic mechanisms have been proposed, such as the amplification of anti-inflammatory signals at the site of damage and the decrease of proinflammatory mediators. It is not advised to administer an antipyretic to every patient who has a fever, despite the temptation to do so. Certain antipyretics can make patients uncomfortable, put them at risk for negative side effects from other drugs they take, or make it difficult to accurately evaluate patients using antibiotics. Acetaminophen and NSAIDs like aspirin, naproxen, and ibuprofen are examples of over-the-counter antipyretics.[25]

4. Conclusion

The hypothalamus thermoregulatory center plays a key role in mediating fever, a complex physiological reaction to pyrogens, which are endogenous or exogenous chemicals that cause the release of cytokines. It supports the immune response by acting as a protective mechanism against inflammation and infection. Recognizing the functions of cytokines such as IL-1, IL-6, and TNF-alpha, which trigger prostaglandin E2 synthesis and raise the hypothalamic set-

point, is essential to an accurate knowledge of the pathophysiology of fever. In order to determine the underlying causes, a comprehensive clinical evaluation that includes a history, physical examination, and the necessary laboratory tests is required for diagnosis. Addressing the underlying cause, controlling symptoms, and offering supportive care—often with antipyretics such acetaminophen or NSAIDs—while being aware of potential side effects are the main goals of treatment. All things considered, a thorough grasp of fever improves clinical judgment, guaranteeing prompt and efficient treatment of patients with fever.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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