Fever is defined as a measured body temperature of at least 38°C (100.4°F). Fever is caused by circulating endogenous and/or exogenous pyrogens that increase levels of prostaglandin E2 (PGE2) in the preoptic area of the hypothalamus. This process increases the physiologic “set point” of body temperature in the hypothalamus. Fever is commonly associated with chills, rigors, sweating, and flushing of the skin. Fever is a symptom of a wide array of diseases; therefore, when evaluating fever, it is important to take an accurate history and review of symptoms. The major etiologies of fever include infectious (most common), non-infectious, neurogenic, drug-induced, and fever of unknown origin. When a fever occurs, a combination of cellular, local, organ-specific, and systemic effects occur and put the individual at risk of both short and long-term dysfunction which, if severe or sustained, may lead to death.

Clinical Features

Fever is defined as a measured temperature of at least 38°C (100.4°F).

Normal body temperature

- Fluctuates in a diurnal variation.
  - Normal fluctuation is between 1-1.3°C (1.8-2.4°F) daily with
    - Lowest noted temperature between 2 AM – 8 AM
Highest noted temperature between 4 AM – 9 PM
- Temperature varies based on the body site used for measurement
  - Rectal vs. oral, etc.
- Normal temperature elevations occur after
  - Vigorous exercise
  - Eating

Clinical features of fever
- Vary according to the cause, but may include
  - Rigors (shivering)
  - Sweats
  - Chills
  - Flushing of skin
  - Tachycardia or palpitations
  - Lethargy

Common Fever Patterns

<table>
<thead>
<tr>
<th>Pattern type</th>
<th>Description</th>
<th>Associated diseases</th>
</tr>
</thead>
</table>

Time course of a typical fever. Image by Lecturio.
<table>
<thead>
<tr>
<th>Fever Type</th>
<th>Description</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous Fever</strong></td>
<td>Temperature continuously remains above normal with daily fluctuations &lt; 1°C (&lt; 33.8°F).</td>
<td>• Typus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Viral pneumonia</td>
</tr>
<tr>
<td><strong>Remittent Fever</strong></td>
<td>Temperature continuously remains above normal with daily fluctuations ≥ 1°C (≥ 33.8°F)</td>
<td>• Typhus</td>
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<tr>
<td></td>
<td></td>
<td>• Sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tuberculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rheumatic fever</td>
</tr>
<tr>
<td><strong>Intermittent Fever</strong></td>
<td>Temperature remains above normal only for a certain period, later returning back to normal.</td>
<td>• Sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pleuritis</td>
</tr>
<tr>
<td><strong>Biphasic Fever</strong></td>
<td>Fever that breaks and returns twice daily.</td>
<td>• Yellow fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dengue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Malaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Typhoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Leptospirosis</td>
</tr>
</tbody>
</table>
Undulant fever

Temperature rises gradually and falls like a wave over days to weeks.

• Brucellosis

Recurrent fever

Days of fever followed by an afebrile period of several days and then a relapse into additional days of fever, usually after 14–21 days.

• Tick-borne fevers

Pel-Ebstein fever

Fever lasting 1-2 weeks followed by 1-2 of an afebrile period.

• Hodgkin lymphoma

Periodical fever

Fever that recurs over months or years; associated with the absence of infection of malignancy.

• Familial Mediterranean fever

Etiology

There are many causes of fever. Several of the most common etiologies are discussed below.

Infectious conditions

- Most common cause of fever
- Produce fever through exogenous pyrogens (discussed below)

Non-infectious disorders

- Produce fever though endogenous pyrogens (discussed below)
- Common causes:
  - Myocardial infarction
  - Pulmonary emboli
  - Neoplasms
  - Trauma
  - Surgery

Neurogenic fever

- Produces fever by direct damage to the hypothalamus from
  - CNS trauma
  - Intracerebral bleeding
  - Increase in intracranial pressure
  - Characterized by a high temperature, resistant to antipyretic therapy, and not associated with sweating

Drug-induced fever
- Produces fever through
  - Interference with the physiological mechanisms of heat loss (from the peripheries) and central temperature regulation
  - Direct damage to tissues
  - Stimulation of an immune response
  - Pyrogenic properties of the drug
- Most common drug classes associated with fever:
  - **Anticonvulsants**
    - Carbamazepine
    - Phenytoin
    - Phenobarbital
  - **Antimicrobials**
    - Minocycline
    - Beta-lactams
    - Sulfonamides
    - Nitrofurantoin
  - **Allopurinol**
  - **Heparin**

**Fever of unknown origin**

Occurs with fever higher than 38.3°C (100.94°F) for at least 3 weeks with an uncertain diagnosis after at least 1 week in the hospital (ie, after extensive evaluation and diagnostic testing). Common causes are

- **Infections**
  - Tuberculosis
  - Intraabdominal abscess
  - Osteomyelitis
  - Bacterial endocarditis
- **Malignancies**
  - Non-Hodgkin lymphoma
  - Leukemia
  - Renal cell carcinoma
- **Systemic autoimmune diseases**
  - Adult Still disease
  - Giant cell arteritis
- **Drugs**

**Common conditions associated with fever**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Influenza, common cold, malaria, HIV, infectious mononucleosis, gastroenteritis</td>
</tr>
</tbody>
</table>
| Medications       | **Prescription:**
                   | Antibiotics, anticonvulsants, narcotics, barbiturates, antihistamines, allopurinol, heparin |
                   | **Illegal drugs:**
                   | Amphetamines, cocaine |
| Trauma or injury  | Heart attack, stroke, heatstroke, heat exhaustion, burns |
| Tissue damage     | From hemolysis, surgery, heart attack, hemorrhage, crush syndrome |
| Neurogenic conditions | CNS trauma, intracerebral bleeding |
| Endocrinopathy    | Hyperthyroidism, pheochromocytoma |
Other
Skin inflammation, arthritis, IBS, blood clots, metabolic disorder, gout, embolism, malignant tumors

Video Gallery

Fever in Adults by Charles Vega, MD

Pathophysiology

Body temperature is regulated by the central nervous system at the level of the hypothalamus.

- **Normal physiologic phenomenon** caused by the release of either exogenous or endogenous pyrogens (any substance that causes fever)
- The hypothalamic thermoregulatory center shifts its set point upwards (similar to the thermostat control in a home).
  - **Circulating pyrogens**
  - ↑ PGE2 in the preoptic area of the hypothalamus

<table>
<thead>
<tr>
<th>Endogenous or pyrogenic cytokines:</th>
<th>Exogenous pyrogens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Produced by inflammation, trauma, or antigen-antibody complexes</td>
<td>• Primary from microbes:</td>
</tr>
<tr>
<td>◦ IL-1</td>
<td>◦ LPS of Gram-negative bacteria</td>
</tr>
<tr>
<td>◦ IL-6</td>
<td>◦ Endotoxins</td>
</tr>
<tr>
<td>◦ TNF-α</td>
<td>◦ Exotoxins</td>
</tr>
<tr>
<td>◦ Interferon gamma</td>
<td>◦ Superantigens</td>
</tr>
<tr>
<td>• Activates the arachidonic acid pathway, which releases prostaglandin E2 (PGE2) → activates the preoptic area of the hypothalamus → increases temperature setpoint</td>
<td>• Binds to macrophages and induces the release of endogenous pyrogens</td>
</tr>
</tbody>
</table>

**Physiologic effects of fever**

- **Heat conservation**: vasoconstriction
  - Increases heat production in the periphery
  - Causes a subjective cold sensation in the hands and feet as blood is shunted from the periphery to internal organs
- **Heat production**: thermogenesis of adipose tissue and muscle
  - Increases core temperature by releasing ATP and heat
  - Muscle heat production → shivering
  - Adipose tissue heat production → prominent in neonates due to a higher percentage of brown fat
- **Behavioral patterns**
  - Seeking warmer rooms
  - Adding extra clothing
  - Reducing activity

**Hypothalamic set-point is reset downward**

- Heat loss occurs through
  - Vasodilation
  - Sweating
  - Behavior changes
- May be due to a reduction in pyrogenic cytokines or the use of antipyretics
Mechanisms of fever generation. A stressor of the body (e.g., infection, injury, trauma) incites lymphocytes to release cytokines which, in turn, stimulate the hypothalamus. Within the hypothalamus, the vascular organ of lamina terminalis, or supraoptic crest (OVLT) activates cyclooxygenases (COX), which catalyzes the formation of prostaglandins (PGE2). These hormone-like substances produce fever by activating cold-sensitive (CS) neurons and inhibiting warm-sensitive (WS) neurons.

**Effects of Fever**

**Beneficial effects**

- Endogenous pyrogens
  - Influence the recruitment and function of many types of immune cells
    - Enhance phagocytosis by neutrophils and macrophages
    - Enhance antigen presentation by macrophages and T cells
  - Decrease the levels of trace metals available (iron and zinc)
    - Helps to inhibit microbial reproduction
- High temperatures: 39–41°C (105.8°F)
  - Directly inhibit the growth of some bacteria
May also inhibit motility and capsule/cell wall formation
- Increases antimicrobial activity of some antibiotics

**Adverse effects**

- Direct cellular damage by cytokines and inflammation
  - Causes both local and systemic effects (summarized in table below)
- Possibility of provoking sepsis syndrome
- Very high fevers: $> 41^\circ C ( > 105.8^\circ F)$
  - Increase host metabolic demands
  - May result in CHF and ischemia

<table>
<thead>
<tr>
<th>Summary of adverse effects of cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular effects</strong></td>
</tr>
<tr>
<td>Membrane, mitochondrial, and DNA damage</td>
</tr>
<tr>
<td>Stimulation of excitotoxic mechanisms</td>
</tr>
<tr>
<td>Protein denaturation</td>
</tr>
<tr>
<td>• Cell death</td>
</tr>
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<td></td>
</tr>
</tbody>
</table>

**Clinical Relevance**

The following conditions are associated with fever and should be considered due to their life-threatening nature.

**DRESS syndrome**

- Drug reaction with eosinophilia and systemic symptoms
- Severe, life-threatening illness with multiorgan dysfunction
- Caused by numerous drugs including
  - Allopurinol
  - Anticonvulsants
  - Sulfonamides
- Symptoms
  - Fever
  - Eosinophilia
  - Diffuse morbilliform rash
  - Lymphadenopathy
  - Atypical lymphocytosis
  - Thrombocytopenia
  - Hepatitis

**Malignant hyperthermia**

- Rare, sudden appearance of fever $> 40^\circ C ( > 105.8^\circ F)$ with muscle rigidity, metabolic acidosis, and hemodynamic instability
- Occurs during general anesthesia
  - Often triggered by succinylcholine

**Neuroleptic malignant syndrome:**

- Presents as high fever, muscle rigidity, altered mental status, and dysautonomia
- Commonly associated with haloperidol
- Occurs due to dopamine depletion from antidopaminergic neuroleptic agents
Serotonin syndrome

- Presents with agitation, confusion, hyperthermia, autonomic hyperactivity, and rigidity
- Associated with SSRIs, especially if combined with linezolid, tramadol, lithium, or any other drugs that inhibit serotonin reuptake in the body

Hyperexia

- Extreme elevation of body temperature > 41.5°C (106.7°F)
- Caused by CNS hemorrhages and severe infections

References

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