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Fever: A Brief Overview

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Abstract: ***This article is an attempt to understand the concept, causes, mechanism, classification, and assessment & management of fever. An essential component of the body's defense against infection is fever. All seven continents are home to the naturally occurring zoonotic disease known as fever. Fever can be classified by its duration as well as the presence or absence of associated symptoms. There are two basic pathways, the hormonal and neural pathways which lead to resetting of the thermoregulatory circuitry. Information from the pyrexia patient is gathered to assess the clinical characteristics of fever. Under proper supervision, the appropriate therapy is given in accordance to manage the fever. This review article will provide a preliminary knowledge about fever for students and scholars. The article looks at the literature that is currently available and demonstrates why fever needs to be considered a global community health issue.***

Keywords: Fever, pyrexia, body temperature, symptoms

Concept of fever (Ogoina, 2011a)
Fever is one of the oldest clinical indicators of disease and one of the most common reasons for medical consultation worldwide. It occurs in response to infection, inflammation and trauma. Fever represents a complex adaptive response of the host to various immune challenges whether infectious or non-infectious. The febrile response is orchestrated by the central nervous system through endocrine, neurological, immunological and behavioural mechanisms.

Definition
The International Union of Physiological Sciences Commission for Thermal Physiological in 2001 defined fever as a state of elevated core temperature, which is often, but not necessarily, a part of the defensive responses of multicellular organism (host) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host.

Thermoregulation
In healthy individuals, body temperature is tightly regulated within a fairly constant range- a thermal set point recently renamed thermal balance point through the process of thermoregulation. The preoptic region of the anterior hypothalamus considered the major thermoregulatory centre in the central nervous system where peripheral and centrally generated temperature signals are received and integrated. (Bligh & Johnson, 1973) (Lim et al., 2008). The preoptic region consists of heat sensitive neurons, namely warm and cold sensitive neurons, which are activated or inhibited in response to temperature changes.

Defining febrile body temperatures
Based on guidelines for management of febrile illnesses provided by authorities such as World Health Organization (WHO) and the Society of Critical Care Medicine and the Infectious Disease Society of America (IDSA), among others, equivalent rectal temperature of 38° (100.4°F) or axillary temperatures of 37.5°C (99.5°F) are indicative of fever in both adults and children. In the geriatric group (>65years), who are likely to have lower body temperatures, IDSA define fever as single oral temperature >100°F (>37.8°C): or repeated oral temperatures >99°F (>37.2°C) or rectal temperatures >99.5°F (37.5°C). of the three major sites (i.e. rectal, oral and axillary) used for temperature assessment, rectal temperature more closely estimates core temperature than oral or axillary temperatures.

Causes of Fever (Morrison et al., 2008) (Rodriguez-Morales et al., 2020)
Infections are the most common cause of fever, but various conditions, illnesses, and medicines can raise the body temperature. These include:

- **Infectious diseases**, e.g., COVID-19, dengue, ebola, gastroenteritis, HIV, influenza, malaria etc.
- **Immunological diseases**, e.g., autoimmune hepatitis, inflammatory bowel diseases, Kawasaki disease, lupus, sarcoidosis etc.
- **Tissue destruction**, as a result of cerebral bleeding, crush syndrome, hemolysis, infarction rhabdomyolysis, surgery, etc.
- **Cancers**, particularly blood cancer such as leukemias and lymphomas;
- **Metabolic disorders**, e.g., gout, and porphyria; and
- **Inherited metabolic disorder**, e.g., Fabry disease.

Symptoms
In addition to raised temperature fever is often characterized by shivering, chills, and shaking, intermittent or excessive sweating, skin flushing, palpitations, feeling weak, dizzy or faint. Systematic symptoms such as headache, lethargy, low appetite, sleepiness, increased pain sensitivity, inability to concentrate and other sickness behaviours may also accompany fever.

Mechanism of fever and febrile response (Mandell et al., 1979) (Cecil et al., 2008) (Fauci, 2008)

In fever the thermal balance point is reset to higher level such that normal peripheral and central body temperatures are now sensed as cold temperature signals by the thermoregulatory circuitry. Generation of fever follows multiple independent afferent and efferent mechanisms depending on the site, nature and severity of inflammation. As the body works towards meeting the new temperature set point, symptoms commonly associated with fever emerge such as shivering, chills, palpitation etc. The various

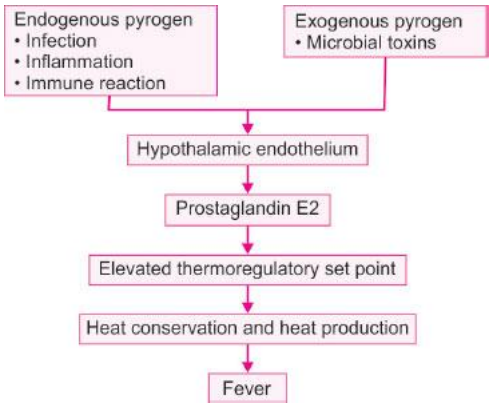
biological molecules involved in the generation of the febrile response and the pathways implicated in these responses are discussed in the following section.

Fever: the role of pyrogens and cryogens

The mechanism of fever appears to be a defensive reaction by the body against disease. When bacteria or viruses invade the body and cause tissue injury, one of the immune system's responses is to produce pyrogens, which directly or inderictly lead to fever. Cryogens on the contrary prevent excessive temperature elevation. Therefore, it is the balance in the interactions between pyrogens and cryogens that determine the height and duration of the febrile response to any immune challenges.

Pyrogens

Pyrogens are classified into exogenous (produced outside the host) and endogenous (produced within the host). Exogenous pyrogens are, essentially, part or whole microorganisms or producs of microorganisms such as toxins. Endogenous pyrogens are mainly pyrogenic cytokines including interleukins IL-6, IL-1, interferon gamma (INF-γ) and tumor necrosis factor (TNF-α). (Mandell et al., 1979) (Davidson, 2002) Endogenous pyrogens are produced by immune cells such as neutrophils, macrophages and lymphocytes as well as by endothelial cells, astrocytes and glial cells in response to exposure to exogenous pyrogens.



Flowchart: Sequence of events in fever (Geitner & Eierman, 2021)

Cryogens

Cryogens include anti-inflammatory cytokines (e.g.IL-10), hormones such as corticotrophin and corticotrophin releasing hormone and many other neuroendocrine products like neuropeptide Y, bombesin, and thyroliberin. They exert anti-pyretic effects by inhibiting synthesis of pyrogenic cytokines (e.g. glucocorticoids),cytokine receptors blockade (e.g. IL-1 receptor antagonist), and increasing heat loss by enhancing sensitivity of warm sensitive neurons (e.g. bombesin), among other mechanism.(Neubauer, 2001)(Roth, 2006)

The fever pathways

Fever signals carried by exogenous and endogenous pyrogens ultimately lead to resetting of the thermoregulatory circuitry via two basic pathways, namely the hormonal and neural pathways.(Ogoina, 2011b) (Dinarello, 1999)(Roth & De Souza, 2001)

The humoral pathway

In this pathway, fever signals carried by pyrogenic cytokines lead to release of prostaglandin E_2 (PGE_2) from the arachidonic acid pathway in cytoplasmic membranes. PGE_2 then activates thermal neurons in the anterior hypothalamus to a higher thermal balance point. (Turrin & Rivest, 2004)(Romanovsky et al., 2006)The febrile response is characterized by an early rapid phase and delayed late phase. The first phase of this febrile response is dependent on PGE_2 synthesized in the liver and lungs before migration to the brain, while the latter phases are due to centrally synthesized PGE_2. Consequently, while peripheral synthesized PGE_2 may act to initiate the febrile response, centrally synthesized PGE_2 may be largely involved in its maintenance.(Steiner et al., 2006) The second humoral pathway is directed by circulating pyrogenic cytokines. They transmit fever signals to the thermoregulatory circuitry by both direct and indirect pathways.

The neural pathway (Blomqvist & Engblom, 2018) (Ding & Li, 2006)

The activation of the neural pathway is believed to be another mechanism by which fever is rapidly initiated. It has been suggested that localised formation of PGE2 at sites of inflammation contribute to fever generation by activating cold-sensitive cutaneous nerves, which, in turn, transmit fever signals to parts of the brain responsible for fever generation.

Classification, types and patterns of fever

Fever can be classified in different ways. One way is the length of time. A fever can be:

- **Acute,** lasting less than 7 days, as in viral upper respiratory tract infection, malaria.
- **Sub-acute,** lasting upto 14 days, as, for example, in typhoid.
- **Chronic or persistent,** lasting over 14 days, as in tuberculosis, HIV, cancers and connective tissue diseases.

Fever can also be classified according to **severity**:

- Low grade
- Moderate
- High
- Hyperpyrexia

Table 1: Normal and febrile body temperature ranges (rectal).(Ogoina, 2011b)

Body temperature	° C	° F
Normal	37-38	98.6-100.4
Mild/low grade fever	38.1-39	100.5-102.2
Moderate grade fever	39.1-40	102.2-104.0
High grade fever	40.1-41.1	104.1-106.0
Hyperpyrexia	>41.1	>106.0

Fevers can also be classified according to the height of temperature.

- **Sustained or continuous**, where it does not fluctuate more than 1.5 °F (1°C) over 24 hours, but is never normal in this time (e.g. thypoid, T.B., bacterial pneumonia).

- **Remittent,** when it fluctuates by more than 2° C but does not become normal (e.g., infective endocarditis, brucellosis).
- **Intermittent,** when the fever occurs for several hours in the day, but not all the time (e.g., malaria, sepsis)**.**
- **Pel-Ebstein fever / Relapsing Fever** are a cyclic fever that is rarely seen in patients with Hodgkin's lymphoma.
- **Undulant fever,** seen in brucellosis.

Typhoid fever is an example of continuous fever and it shows a characteristic step-ladder pattern, a step-wise increase in temperature with high plateau.(Barnett, 2016)

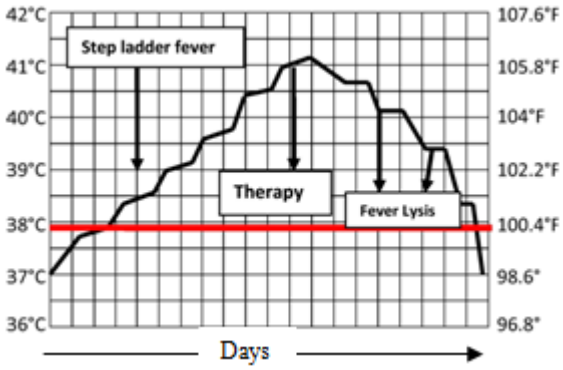


Figure 1: Continuous step ladder pattern of fever classical of typhoid fever

Among the types of intermittent fever are one specific to cases of malaria caused by different pathogens. This are-

- **Quotidian fever,** with a 24-hour periodicity, typical of malaria caused by *Plasmodium knowlesi* (*P. knowlesi*)
- **Tertian fever,** with a 48-hour periodicity, typical of later course malaria caused by *Plasmodium falciparium*, *P.vivax*, or *P.ovale*;
- **Quartan fever,** with a 72-hour periodicity, typical of later course malaria caused by *P. malariae.*

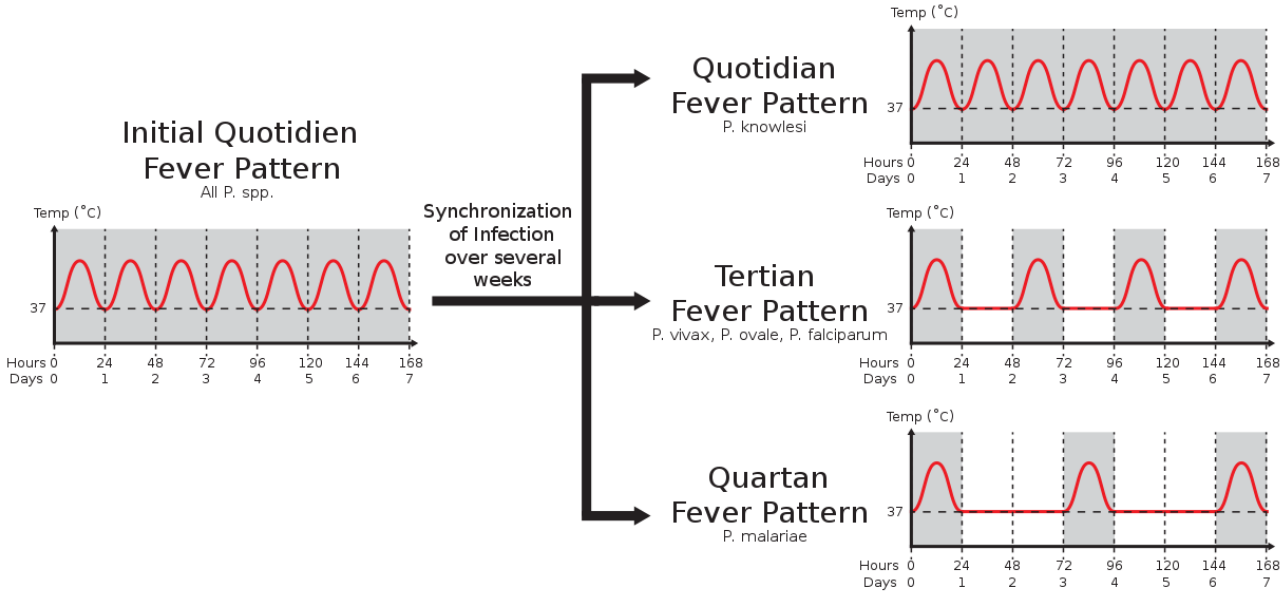


Figure 2: Different fever patterns observed in Plasmodium infections
Source: https://commons.wikimedia.org/wiki/File:Fever_Patterns_v1.1.svg

Management of fever

For general treatment of fever there are two methods of anti-pyresis. These are: Non Pharmacological and Pharmacological Therapy.

Non Pharmacological

Isolation and rest

- Continuous observation and examination
- Provide adequate nutrition and fluids to meet the increased metabolic demands and prevent dehydration.
- Provide tepid sponge bath to increase heat loss through conduction.

Pharmacological Therapy

- Paracetamol, Ibuprofen
- The debilitating symptoms are treated by Non-steroidal anti-inflammatory drugs (NSAIDS) and Glucocorticoids.

Seek emergency help if patient:

- Unresponsive
- Wheezing or has difficulty breathing.

- Appearing blue in the lips.
- Having convulsions or seizures.
- Speaking in a confused or altered way.
- A fever combined with stiff neck.
- Fever with sudden onset of rash.
- Temperature above 105 ° F.

Assessment & initial management of acute undifferentiated fever. (Bhargava et al., 2018)(Paul et al., 2022)

Step 1: Collect epidemiological information

- Local disease prevalence, seasonality (malaria, arboviral infections, scrub typhus, leptospirosis), potential exposure to animals, vectors (mosquitoes, mites).
- Consider host factors: age, comorbidities, immunosuppression, and pregnancy.

Step 2: Evaluate clinical features

- Assess for severity and triage. Rule out localized infections.
- Consider key features: Onset, duration and course of fever, key rule-in and rule-out features, and characteristic pattern of organ involvement.

Step 3: Perform first-line and, if possible, confirmatory diagnostic tests

- Rule out malaria by smear microscopy and rapid diagnostic tests.
- Rule out influenza if currently active in the region.
- Evaluate non-malarial acute undifferentiated febrile illness (AUFI) with full blood count, urine analysis, biochemical tests, and imaging if clinically indicated. Definitive tests, if available: isolation (enteric fever), antigen detection (dengue), serology (rickettsial, leptospirosis).

Step 4: Integrate information from steps 1, 2, 3 to formulate confirmed or probable diagnosis.

- Initiate empirical therapy based on setting and severity of illness.
- For severely ill patients with non-malarial, non-arboviral AUFI, usage of a combination of 3rd generation cephalosporin + doxycycline as empirical therapy to cover rickettsioses, leptospirosis and enteric fever.

Step 5: Monitor patient for therapeutic response, follow up test results

- Monitor response to therapy. Modify therapy according to results of definitive tests.
- Review diagnosis and evaluate for other infections if fever persistent.

Conclusion

Fever is recognized as an ancient adaptive compensatory defense mechanism leading to immune activation, decrease in bacterial and viral growth rate, and improve host survival in response to invasion by foreign antigen.(Russell et al., 2003) In view of its integral role in the pathogenesis of diseases, fever will remain a cardinal manifestation of old, new and emerging diseases, whether infectious or non-infectious. It is therefore imperative for scientists and clinicians alike to continue to harness and expand knowledge gained so far in the understanding of the febrile response in order to improve on the diagnosis, prevention and management of the numerous diseases characterized by fever.

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