

Fever and Hyperthermia

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapters 17, 18, 19, and e-5)

Definition

- Fever
 - An elevation of normal body temperature in conjunction with an increase in the hypothalamic set point
 - Infectious causes are common.
- Hyperthermia
 - An unchanged setting of the hypothalamic set point in conjunction with an uncontrolled increase in body temperature that exceeds the body's ability to lose heat
 - Heat stroke
 - Thermoregulatory failure in association with a warm environment
 - Malignant hyperthermia
 - Hyperthermic and systemic response to halothane and other inhalational anesthetics in patients with genetic abnormality
 - Neuroleptic malignant syndrome
 - Syndrome of hyperthermia, autonomic dysregulation, and extrapyramidal side effects caused by neuroleptic agents (e.g., haloperidol)
- Hyperpyrexia
 - Temperature $>41.5^{\circ}\text{C}$ ($>106.7^{\circ}\text{F}$)
 - Can occur with severe infections, but more commonly occurs with central nervous system (CNS) hemorrhages or hyperthermia

Epidemiology

- The incidence of fever is not known precisely, but fever is one of the most common presenting symptoms in clinical practice.
- In the U.S., 7000 deaths were attributed to heat injury in 1979–1997.

Mechanism

- Fever
 - Microbial structural components and toxins, antigen-antibody complexes, complement components, and probably other molecules (as yet unidentified) are all capable of stimulating leukocytes and endothelial cells to produce pyrogenic cytokines, including:
 - Interleukin (IL)-1
 - IL-6
 - Tumor necrosis factor
 - Interferon

- These cytokines act on the hypothalamic endothelium to elevate the thermoregulatory set point, thus causing fever.
- Hyperthermia
 - 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 dissipate it.
 - Malignant hyperthermia
 - Occurs in individuals with an inherited abnormality of skeletal-muscle sarcoplasmic reticulum that causes a rapid increase in intracellular calcium levels in response to halothane and other inhalational anesthetics or to succinylcholine
 - Neuroleptic malignant syndrome
 - Appears to be caused by inhibition of central dopamine receptors in the hypothalamus, resulting in increased heat generation and decreased heat dissipation

Symptoms & Signs

- Temperature
 - The mean normal oral temperature is $36.8^{\circ} \pm 0.4^{\circ}\text{C}$ ($98.2^{\circ} \pm 0.7^{\circ}\text{F}$), with low levels at 6 a.m. and high levels at 4–6 p.m.
 - The normal daily temperature variation is typically 0.5°C (0.9°F).
 - However, in some individuals recovering from a febrile illness, daily variation can be as great as 1.0°C .
 - During a febrile illness, diurnal variations are usually maintained, but at higher levels.
 - Daily temperature swings do not occur in patients with hyperthermia.
 - Rectal temperatures are generally 0.4°C (0.7°F) higher than oral readings.
 - Lower oral readings are probably attributable to mouth breathing, a particularly important factor in patients with respiratory infections and rapid breathing.
 - Lower-esophageal temperatures closely reflect core temperature.
 - Tympanic thermometer measurements, although convenient, may be more variable than directly determined oral or rectal values.
- Some febrile diseases have characteristic patterns.
 - With relapsing fevers, febrile episodes are separated by intervals of normal temperature.
 - Tertian fevers are associated with paroxysms on the first and third days.
 - *Plasmodium vivax* causes tertian fevers.
 - Quartan fevers are associated with paroxysms on the first and fourth days.
 - *P. malariae* causes quartan fevers.
 - Other relapsing fevers are related to *Borrelia* infections and rat-bite fever, which are both associated with days of fever followed by a several-day afebrile period and then a relapse.
 - Pel-Ebstein fever, with fevers lasting 3–10 days separated by afebrile periods of 3–10 days, is classic for Hodgkin's disease and other lymphomas.
 - In cyclic neutropenia, fevers occur every 21 days and accompany the neutropenia.
 - There is no periodicity of fever in patients with familial Mediterranean fever.
- Signs of hyperthermia
 - Hallucinations

- Delirium
- Dry skin
- Pupil dilation
- Muscle rigidity

Differential Diagnosis

Fever vs hyperthermia

- It is important to distinguish between fever and hyperthermia.
 - Hyperthermia can be rapidly fatal and characteristically does not respond to antipyretics.
- There is no rapid way to make this distinction.
- Hyperthermia is often diagnosed on the basis of events immediately preceding elevation of core temperature.
 - Heat exposure
 - Treatment with drugs that interfere with thermoregulation
- In addition to clinical history, physical aspects of some forms of hyperthermia may alert the clinician.
 - In heat-stroke syndromes and in the setting of drugs that block sweating, the skin is hot but dry.
 - Antipyretics do not reduce elevated temperature in hyperthermia.
 - In fever and hyperpyrexia, adequate doses of aspirin or acetaminophen usually result in some decrease in body temperature.

Causes of hyperthermia syndromes

- Heat stroke: thermoregulatory failure in association with a warm environment
 - Exertional: caused by exercise in high heat or humidity
 - Even in healthy individuals, dehydration or common medications (e.g., over-the-counter antihistamines with anticholinergic side effects) may help to precipitate exertional heat stroke.
 - Nonexertional: occurs in high heat or humidity
 - Typically affects very young, elderly, or bedridden individuals, particularly during heat waves
 - Also affects patients taking anticholinergic agents (e.g., phenothiazines), antiparkinsonian drugs, diuretics
- Drugs
 - Monoamine oxidase inhibitors (MAOIs)
 - Tricyclic antidepressants
 - Amphetamines
 - Cocaine
 - Phencyclidine
 - "Ecstasy" (methylenedioxymethamphetamine)
 - Lysergic acid
 - Diethylamide
 - Salicylates
 - Lithium
 - Anticholinergic agents
- Malignant hyperthermia
 - Elevated temperature, increased muscle metabolism, muscle rigidity, rhabdomyolysis, acidosis, and cardiovascular instability develop rapidly.

- Occurs with use of inhalational anesthetics or succinylcholine
- Often fatal
- Neuroleptic malignant syndrome
 - Characterized by "lead-pipe" muscle rigidity, extrapyramidal side effects, autonomic dysregulation, and hyperthermia
 - Occurs in the setting of:
 - Neuroleptic agent use
 - Phenothiazines
 - Butyrophenones, including haloperidol and bromperidol
 - Fluoxetine
 - Loxapine
 - Tricyclic benzodiazepines
 - Metoclopramide
 - Domperidone
 - Thiothixene
 - Molindone
 - Withdrawal of dopaminergic agents
- Serotonin syndrome
 - Seen with selective serotonin uptake inhibitors (SSRIs), MAOIs, tricyclic antidepressants, and other serotonergic medications
 - Has many overlapping features, including hyperthermia, but is distinguished by diarrhea, tremor, and myoclonus
- Endocrinopathy
 - Thyrotoxicosis
 - Pheochromocytoma
- CNS damage
 - Cerebral hemorrhage
 - Status epilepticus
 - Hypothalamic injury

Diagnostic Approach

- Few signs and symptoms in medicine have as many possible diagnoses as fever.
- The tempo and complexity of the workup will depend on the pace of the illness, diagnostic considerations, and the patient's immune status.
- If findings are focal or if the history, epidemiologic setting, or physical examination suggests certain diagnoses, the laboratory examination can be focused.
- If fever is undifferentiated, the diagnostic net must be cast further.
- A meticulous history is most important.
- Attention must be paid to :
 - Prescription and nonprescription drugs (including supplements and herbs)
 - Surgical or dental procedures
 - Exact nature of prosthetic materials and/or implanted devices
 - Occupational information concerning exposure to:
 - Animals
 - Toxic fumes
 - Potentially infectious agents
 - Possible antigens
 - Febrile or infectious individuals in the home, workplace, or school
 - Geographic area in which the patient has lived
 - Travel history (including military service)

- Information on:
 - Unusual hobbies
 - Dietary proclivities (e.g., raw or poorly cooked meat, raw fish, unpasteurized milk or cheeses)
 - Household pets
 - Sexual orientation, including precautions taken or omitted
 - Use of tobacco, alcohol, and marijuana or other illicit drugs
 - Trauma
 - Animal bites
 - Tick or other insect bites
 - Transfusions
 - Immunizations
 - Drug allergies or sensitivities
 - Ethnic origin
 - Blacks are most likely to have hemoglobinopathies.
 - Turks, Arabs, Armenians, and Sephardic Jews are especially likely to have familial Mediterranean fever.
- Information on family members with:
 - Tuberculosis
 - Other febrile or infectious diseases
 - Arthritis or collagen vascular disease
 - Unusual family symptomatology, such as deafness, urticaria, fevers and polyserositis, bone pain, or anemia
- Physical examination should include:
 - Determination of oral or rectal temperature
 - Examination of:
 - Skin
 - Lymph nodes
 - Eyes
 - Nail beds
 - Cardiovascular system
 - Chest
 - Abdomen
 - Musculoskeletal system
 - Nervous system
 - Rectum
 - In men: examination of penis, prostate, scrotum, and testes
 - The foreskin, if present, should be retracted.
 - In women: pelvic examination, looking for causes of fever such as pelvic inflammatory disease and tubo-ovarian abscess

Laboratory Tests

- If history, epidemiologic situation, or physical examination suggests more than a simple viral infection, the following tests may be indicated:
 - Complete blood count
 - Differential count
 - Perform manually or with an instrument sensitive to the identification of eosinophils, juvenile or band forms, toxic granulations, and Döhle bodies

- Blood smear
 - Appropriate if there is a history of exposure or possible exposure to a variety of pathogens, including:
 - Malaria parasites
 - *Babesia*
 - *Ehrlichia*
 - *Borrelia*
 - Trypanosomes
- Erythrocyte sedimentation rate
 - Extremely high values (> 100 mm/h) may suggest a primary rheumatologic disorder, vasculitis, or malignancy.
- Urinalysis, with examination of urinary sediment
- Chemistries
 - Electrolytes
 - Glucose
 - Blood urea nitrogen
 - Creatinine
 - Liver function
 - Creatine phosphokinase (elevated in hyperthermia) or amylase
- Microbiologic tests
 - Rapid streptococcal test or throat culture if there is pharyngitis
 - Cultures of blood and urine
 - Stain, fluid analysis, and culture of samples from specific sites of concern identified by history and examination
 - Sputum analysis in patients with suspected pneumonia
 - Joint fluid analysis in patients with arthritis
 - Cerebrospinal fluid analysis in patients with suspected meningitis
 - HIV test in patients at epidemiologic risk

Imaging

- Chest x-ray
 - Part of the evaluation of any significant febrile illness
- Other imaging studies: guided by symptoms and signs

Diagnostic Procedures

- Lumbar puncture
 - Indicated in patients with possible bacterial meningitis
- Aspiration and drainage of possibly infected collections or abscesses
 - Often done with radiologic guidance
- Bone marrow biopsy (not simple aspiration) for histopathologic studies (as well as culture)
 - Indicated in febrile syndromes when marrow infiltration by pathogens or tumor cells is possible

Treatment Approach

- Treatment of fever
 - Objectives
 - To reduce the elevated hypothalamic set point
 - To facilitate heat loss

- Treatment to reduce fever is recommended for:
 - Patients with cardiac, cerebrovascular, or pulmonary insufficiency
 - Patients with organic brain disease
 - Children with a history of febrile or nonfebrile seizures
 - There is no correlation between absolute temperature elevation and onset of a febrile seizure in susceptible children.
- Antipyretic treatment should be given on a regular schedule rather than intermittently.
 - Intermittent therapy aggravates chills and sweats.
 - Chronic high-dose therapy with antipyretics (such as aspirin or nonsteroidal anti-inflammatory drugs [NSAIDs] used in arthritis) does not reduce normal core body temperature.
- Treatment of hyperthermia
 - Objectives
 - To facilitate heat loss
 - To reduce heat production in endogenous hyperthermia

Specific Treatments

Fever

- Antipyretic treatment
 - Aspirin, NSAIDs, and glucocorticoids are effective antipyretics.
 - Acetaminophen is preferred because it:
 - Does not mask signs of inflammation
 - Does not impair platelet function
 - Does not adversely affect the GI tract
 - Is not associated with Reye's syndrome
 - Treating fever and its symptoms does no harm and does not slow the resolution of common viral and bacterial infections.
 - Reducing fever with antipyretics also reduces systemic symptoms of headache, myalgias, and arthralgias.
- In hyperpyrexia, the use of cooling blankets facilitates the reduction of temperature.
 - However, cooling blankets should not be used without oral antipyretics.

Hyperthermia

- Antipyretics are of no use in hyperthermia.
- Physical cooling should be initiated immediately.
 - A sponge bath with cool water, coupled with the use of fans, is often sufficient.
 - Cooling blankets and ice baths are effective but not well tolerated.
 - Intravenous fluid administration
 - Internal cooling by gastric or peritoneal lavage with iced saline in severe cases
 - In extreme cases, hemodialysis or cardiopulmonary bypass
- Malignant hyperthermia
 - Cessation of anesthesia
 - Administration of dantrolene (1–2.5 mg/kg q6h for at least 24–48 hours) **plus**
 - Procainamide administration because of risk of ventricular fibrillation

- Neuroleptic malignant syndrome
 - Discontinuation of offending agents
 - Pharmacotherapy not well studied
 - Efficacy has been questioned.
 - Potential agents include:
 - Dantrolene (0.25–2 mg/kg q6–12h IV)
 - Bromocriptine (2.5–10 mg PO or via nasogastric tube q6–8h)
 - Amantadine (200 mg PO or via nasogastric tube q12h)

Monitoring

- Monitoring of patients with fever depends on the underlying cause.
- Patients with hyperthermia generally require admission to a monitored-care setting until cooling measures have restored normothermia.

Complications

- Complications are related to the underlying cause of fever.
- Hyperthermia is often fatal.

Prognosis

- Fever
 - In most cases, either the patient recovers spontaneously or the history, physical examination, and initial screening laboratory studies lead to a diagnosis.
 - When fever continues for 2–3 weeks and repeat examinations and laboratory tests are unrevealing, the patient is provisionally diagnosed as having fever of unknown origin.
- Hyperthermia
 - The prognosis for hyperthermia depends on the rapidity of cooling.

Prevention

- Fever
 - No common preventive measures
- Hyperthermia
 - Avoid excessive activity in hot or humid environments.
 - Maintain adequate intake of fluids before, during, and after strenuous activity or exposure to extreme heat.
 - Maintain proper ventilation to promote cooling from sweat evaporation.

ICD-9-CM

- 778.4 Other disturbances of temperature regulation of newborn
- 780.6 Fever and Hyperthermia

See Also

- Fever of Unknown Origin

Internet Sites

- Professionals
 - Homepage
National Institute of Allergy and Infectious Diseases
- Patients
 - Fever
MedlinePlus

General Bibliography

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PEARLS

- Fever due to malaria in returning travelers typically does not follow a classic tertian or quartan pattern because of the asynchronous release of merozoites early in infection.
- The Jarisch-Herxheimer reaction consists of fever—and, in extreme cases, a sepsis syndrome—occurring shortly after initiation of antimicrobial therapy.
 - Due to release of endogenous pyrogens from dying organisms
 - Best described during treatment of tertiary syphilis
 - Also may occur during therapy for brucellosis, enteric fever (typhoid), borreliosis (relapsing fever), schistosomiasis, and trypanosomiasis
- Linezolid is increasingly used for treatment of a variety of gram-positive bacterial infections, particularly those caused by drug-resistant enterococcal and staphylococcal species.
 - Because of the potential for serotonin syndrome, use of linezolid is contraindicated in conjunction with a variety of antidepressants, especially the SSRIs.
- Hectic fever is common after subarachnoid hemorrhage and often does not reflect infection.
- Commonly used drugs capable of causing fever include anticonvulsants (phenytoin), allopurinol, and many antibiotics, most commonly β -lactam agents and sulfa drugs.