Pathomechanism of fever. Fever of unknown origin. Fever and rash

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Regulation of body temperature

- Controlled by the hypothalamus
- Signals are received
  - from peripheral nerves (transmit information from warmth/cold receptors)
  - from the temperature of the blood bathing the region
- In a neutral temperature environment, the metabolic rate of human produces more heat than necessary to maintain the core temperature at 37°C
- Thermoregulatory center balances the heat production derived from metabolic activity in muscle and the liver with heat dissipation from the skin, and lungs
Alterations in body temperature

Normal temperature:

Oral 36.8°C ± 0.5°C

Rectal 0.4°C higher than oral readings

Tympanic membrane (unadjusted mode) 0.8°C lower than rectal

Fever: an a.m. temperature of >37.2°C or a p.m. temperature of >37.7°C

Hyperpyrexia: >41.5°C

Hypothermia: <35°C rectal temperature

The normal daily temperature variation is typically 0.5°C
- with lowest level at 6 a.m. and highest level at 4-6 p.m.
- During a febrile illness, the diurnal variation is usually maintained a higher, febrile levels
Pathogenesis of fever

- Fever is an elevation of body temperature that occurs in conjunction with an increase in the hypothalamic set point.
  - Neurons in vasomotor center are activated and vasoconstriction occurs in the hands and feet (decreased heat loss from the skin, and the patient feels cold)
  - Shivering, which increases heat production from the muscles, starts
  - Non-shivering heat production from the liver
  - Behavioral adjustments (putting on more clothing) also decreases heat loss
Pathogenesis of fever

- **Pyrogen** – substance that causes fever
  - **Exogen pyrogens**: microbial products, toxins, or whole microorganisms
    - Endotoxins produced by all gram-negative bacteria
    - Superantigens: pyrogenic products of gram-positive bacteria (enterotoxins of Staphylococcus aureus and the group A and B streptococcal toxins)
  - **Pyrogenic cytokines**
    - **Endogen pyrogens** (IL-1, IL-6, TNF, interferon-alpha etc.)
      - Bacterial and fungal products, as well as viruses induce the synthesis and release of pyrogenic cytokines
      - Other inflammatory processes, trauma, tissue necrosis without microbial infection can also induce endogen pyrogen production.
  - Pyrogens induce \( \text{PGE}_2 \) synthesis in the peripheral tissues (myalgias, arthralgias) – elevation of \( \text{PGE}_2 \) in the brain – rapid release of cyclic AMP in the hypothalamus – activation of neuronal endings from the thermoregulatory center
Hyperthermia

- Uncontrolled increase in body temperature that exceeds the body’s ability to lose heat. The setting of the hypothalamic thermoregulatory center is unchanged.
  - Heat stroke
    - Exertional: in individuals exercising at elevated ambient temperature and/or humidity
    - Nonexertional: in very young or elderly individuals, particularly during heat waves.
  - Drug induced
    - Result of the use of psychotropic and illicit drugs (MAOIs, ecstasy, cocaine, amphetamines)

- Malignant neuroleptic syndrome
  - Neuroleptic agent use (phenothiazines, haloperidol, metoclopramide). Muscle rigidity, extra pyramidal side effects, autonomic dysregulation, and hyperthermia
  - Serotonin syndrome
    - SSRI. Clinical features: similar to the malignant neuroleptic syndrome, but may be distinguished by the presence of diarrhea, tremor, and myoclonus
Treatment of fever and hyperthermia

- Treatment of fever and its symptoms does no harm and does not slow the resolution of common viral and bacterial infections.

- In bacterial infections, withholding antipyretic therapy can be helpful in evaluating the effectiveness of the antibiotic therapy.

- Withholding antipyretics in some cases may facilitate the diagnosis of an unusual febrile disease.

- Hyperthermia does not respond to antipyretics. Physical cooling (external and internal). Dantrolene iv. or orally.
Types of fever

Continuous fever

The daily temperature variation is < 1°C
Typhoid fever and lobar pneumonia
Types of fever (bacteriaemia- microabscess, septic fever)

**Remittent fever**

The daily variation of body temperature is $> 1^\circ C$

The lowest body temperature $> 37^\circ C$

**Intermittent fever**

The daily variation of body temperature is $> 1^\circ C$

The lowest body temperature $< 37^\circ C$
Types of fever (relapsing fever)

Fever lasting 3-10 days is followed by afebrile periods of 3-10 days. (Pel-Ebstein pattern). Hodgkin’s disease, other lymphomas.

Plasmodium vivax causes fever every third day. Plasmodium malariae causes fever every fourth day.

Borellia infection
Definition and classification of FUO

Classic Fever of Unknown Origin

- Temperatures of $> 38.3 \, ^\circ C$ ($> 10 \, ^\circ F$) on several occasions
- Duration of fever is more than 3 weeks
- Three outpatient visits or 3 days in the hospital without elucidation of a cause or 1 week of “intelligent and invasive” ambulatory investigation
Definition and classification of FUO

Nosocomial FUO
- Temperatures of $> 38.3 \, ^\circ\text{C} \, (> 10 \, ^\circ\text{F})$ on several occasions in a hospitalized patient
- Three days of investigation, including 2 days’ incubation of cultures

Neutropenic FUO
- Temperatures of $> 38.3 \, ^\circ\text{C} \, (> 10 \, ^\circ\text{F})$ on several occasions in a patient whose neutrophil count is $< 500/\mu\text{L}$
- A specific cause is not identified after 3 days of investigation, including at least 2 days’ incubation of cultures

HIV-associated FUO
- Temperatures of $> 38.3 \, ^\circ\text{C} \, (> 10 \, ^\circ\text{F})$ on several occasions over a period of $> 4$ weeks for outpatients or $> 3$ days for hospitalized patients with HIV infection
- Appropriate investigation over 3 days, including 2 days’ incubation of cultures
## Classic FUO in adult patients

<table>
<thead>
<tr>
<th>Disease-groups</th>
<th>Cases(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>26</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>13</td>
</tr>
<tr>
<td>Multisystem diseases (SLE, RA, vasculitis, granulomatous diaseases)</td>
<td>24</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>25-30</td>
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</tbody>
</table>

The leading infectious causes of FUO

- Extrapulmonary tuberculosis
- Mononucleosis syndromes (EB, CMV) or HIV sometimes confounded by delayed antibody responses
- Intraabdominal abscesses
- Osteomyelitis (especially where prosthetic devices have been implanted)
- Endocarditis
- Fungal disease (histoplasmosis)
Noninfectious inflammatory diseases in the background of FUO

- Giant-cell arteritis (>50 years of age, this disease accounts for 15-20% of FUO cases)
- Still’s disease: leukocytosis, anemia, arthralgias, polyserositis, lymphadenopathy, splenomegaly, rash
- SLE
- Granulomatous diseases
  - Sarcoidosis
  - Crohn’s disease
  - Granulomatous hepatitis
Miscellaneous causes of FUO in adults

- Drug fever
  - β-lactam antibiotics
  - Cardiovascular drugs (quinidine)
  - Antineoplastic drugs
  - Drugs acting on the central nervous system (phenytoin)

- Pulmonary embolism

- Factitious fever
  - In young women in the health professions

- Hereditary periodic fever syndromes
General considerations in adult FUO

- The FUO is a rare condition.
- As the duration of fever increases, the likelihood of an infectious cause decreases.
- In cases of infectious origin, the cause is not a rare infectious disease, rather the unusual manifestation of a common infectious disease.
- In the elderly patients, multisystem disease is the most frequent cause of FUO.
Approach to the patient with classic FUO

- History (environmental, occupational, and professional)
- Physical exam
- Erythrocyte sedimentation rate and CRP should be determined
- Routine blood chemistry (incl. complete blood count, liver function tests and serum bilirubin, serum creatinine, electrolytes, muscle enzymes, serum protein electrophoresis)
- ANA, RF, VDRL, HIV, EBV, CMV, skin test to screen for tuberculosis
- Hepatitis serology (if liver tests are positive)
- Multiple blood samples (3-6), including samples for anaerobic culture
- Urine analysis and cultures
- Chest X-ray
Striking elevation (>100 mm/1. h) of ESR and FUO

- 58% neoplasm
  - Lymphoma
  - Multiple myeloma
  - Metastatic colon or breast cancer
- 28% infection or multisystem inflammatory disease
  - Endocarditis
  - Rheumatoid arthritis or giant cell arteritis or polymyalgia rheumatica, Still’s disease (leukocytosis, anemia, arthralgias, polyserositis, lymphadenopathy, splenomegaly, rash)
Noninvasive and invasive procedures in patients with FUO

- **Colonoscopy** (to exam terminal ileum and cecum)
- **Bronchoscopy**, bronchoalveolar lavage for culture and cytology
- **Ultrasonography**: investigation of hepatobiliary tract, kidneys, spleen, etc.
- **Echocardiography**: bacterial endocarditis, pericardial fluid, atrial myxomas
- **High resolution spiral CT (MRI)** of chest and abdomen with iv. and oral contrast
  - Abdomen: abscess, hematoma, lymphadenopathy
  - Chest: sarcoidosis, lymphoma, pulmonary cancer, fungal infection
  - Angio-CT: saccular aneurysma may be seen (most commonly in renal or hepatic vessels) – diagnosis of arteritis
- **Radionuclide scanning**
  - Gallium67 citrate, or indium111 labeled leukocyte scintigraphy
    - It is suggested to use if no specific organ is suspected of being abnormal
    - False-positive and false-negative findings are common
- **Fluorodeoxyglucose PET scanning** appears superior to other forms of nuclear imaging (FDG accumulates in tumor and at sites of inflammation and vasculitis)
Approach to the patient with classic FUO

- Anamnesis
  - Occupational and professional history
  - Travel history
  - Environmental history
  - Previous and present medication

- Physical and laboratory examinations
  - Comprehensive, repeated physical examination
  - The basic laboratory testing and radiological examination
  - In case of presence of a potentially diagnostic clue (key finding in the history, localized signs, or key symptoms) directed examinations
  - No potentially diagnostic clue: CT, MRI, $^{67}$Ga scan, FDG PET scan, needle biopsy, invasive testing
FUO in immunocompromised patients

**HIV-associated FUO**
- 80% infection (due to *Mycobacterium avium* or *Mycobacterium intracellulare*, tuberculosis, *Pneumocystis*, cryptococcosis, CMV, etc.)
- 8% neoplasm, mostly non-Hodgkin lymphoma
- Drug fever

**Neutropenic FUO**
- Neutropenic patients are susceptible to focal bacterial and fungal, to bacteremic infection, to infections involving catheters and to perianal infections.
- 50-60% of febrile neutropenic patients are infected, and 20% are bacteremic.
- Fever even after the recovery from neutropenia suggest systemic fungal infection (Candida, aspergillus)
Classification of rash that reflect systemic disease

- Not palpable, flat lesion defined by an area of changed color (blanchable erythema): **macula**
- Elevated, solid skin lesions:
  - **Papula**: < 5 mm
  - **Plaque**: > 5 mm with a flat, plateau-like surface
  - **Nodulus**: > 5 mm in diameter with a more rounded configuration
- **Urticaria**: are papules or plaques that are pale pink and may appear annular (ringlike). Transient, lasting only 24-48 h in a defined area
- Skin-bleedings
  - **Petechea**: nonpalpable, flat lesion, < 3 mm in diameter
  - **Ecchymosis**: nonpalpable, flat lesion, > 3 mm
  - **Palpable purpura**: a raised lesion that is due to inflammation of the vessel wall with subsequent hemorrhage.
- Elevated lesions containing fluid:
  - **Vesicula**: < 5 mm, elevated, circumscribed lesion,
  - **Bulla**: > 5 mm
  - **Pustula**: raised lesion containing purulent exudate
Paramyxovirus (first disease). Discrete maculopapulous lesions that become confluent as rash spreads from hairline downward, sparing palms and soles. Clinical syndrome: fever, cough, conjunctivitis, coryza.
In young adults cervical lymphadenopathy, pharyngitis, hepatosplenomegaly, atypical lymphocytosis, heterophile antibodies (in appr. 50% of university students are present)
Mild fever and arthritis in adult. Rash following resolution of fever. Maculo-reticularis eruption first on the extremities, thereafter on the trunk.
Causes:

- Streptococcal, mycobacterium or Yersinia infections
- Drug-induced (penicillin, contraceptives)
- Sarcoidosis

Arthralgy in 50% of cases
Drug intake (sulfa, phenytoin, penicillin; Herpes simplex virus Mycoplasma pneumoniae

Characteristic target lesions of the palm in erythema multiforme begin with a central vesicle.

Erythema migrans with central clearing and a necrotic center.

Courtesy of Dori F Zaleznik, MD.
Giant urticaria

Very large erythematous annular lesion of the shoulder with central clearing. This patient had several large lesions of this type which could be confused with erythema migrans.

*Courtesy of Lee T Nesbitt, Jr. The Skin and Infection: A Color Atlas and Text, Sanders, CV, Nesbitt, LT Jr (Eds), Williams & Wilkins, Baltimore, 1995.*

[http://www.lww.com](http://www.lww.com)
Dermatomal herpes zoster

Grouped vesicles on an erythematous base present in a dermatomal distribution on the upper back due to Herpes zoster. The lesions stop abruptly at the midline.

*Courtesy of Lee T Nesbitt, Jr. The Skin and Infection: A Color Atlas and Text, Sanders, CV, Nesbitt, LT Jr (Eds), Williams & Wilkins, Baltimore, 1995.*

[http://www.lww.com](http://www.lww.com)
Vesicular lesions on an erythematous base are characteristic of chickenpox. The lesions occur in crops and are present in a variety of stages from maculopapular to vesicular or even pustular. Central necrosis and early crusting is also visible.

_Courtesy of Lee T Nesbitt, Jr. The Skin and Infection: A Color Atlas and Text, Sanders, CV, Nesbitt, LT Jr (Eds), Williams & Wilkins, Baltimore 1995._

_http://www.lww.com_
Multiple grouped vesicles of genital herpes on the shaft of the penis. These lesions are frequently painful.

*Courtesy of Larry Millikan. (The Skin and Infection: A Color Atlas and Text, Sanders, CV, Nesbitt, LT Jr (Eds), Williams & Wilkins, Baltimore, 1995. [http://www.lww.com](http://www.lww.com)*
Hot tub folliculitis

This form of folliculitis is caused by Pseudomonas aeruginosa and can occur after exposure to hot tubs or whirlpools. Courtesy of Charles V Sanders. (The Skin and Infection: A Color Atlas and Text, Sanders, CV, Nesbitt, LT Jr (Eds), Williams & Wilkins, Baltimore, 1995). http://www.lww.com
Skin manifestation of DIC. (In splenectomized patients S. pneumoniae and H. infection can also cause)
Extensive maculopapular and petechial lesions on the trunk and thigh in a patient with Rocky Mountain spotted fever. The rash characteristically begins on the wrists and ankles and spreads centripetally.

*Courtesy of Harold G Muchmore. (The Skin and Infection: A Color Atlas and Text, Sanders, CV, Nesbitt, LT Jr (Eds), Williams &Wilkins, Baltimore, 1995. [http://www.lww.com](http://www.lww.com)*