# Fever of Unknown Origin

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# Fever "Pyrexia"

#### **Physiology Definition:**

The International Union of Physiological Sciences Commission for Thermal Physiology define Fever as:

 $\bigtriangledown$ 

"a state of elevated core temperature, which is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host

#### **Clinical Definition:**

According to Harrison's Principles of Internal Medicine, fever is defined as a core temperature (rectal) of 37.5°C–38.3°C (99.5°F–100.9°F), a skin temperature (axillary) >37.2°C (>99°F), a morning oral temperature >37.2°C (>99°F), or late afternoon oral temperature >37.7°C (>99.9°F), with lower thresholds applicable to frail elderly persons

So A fever is usually when your body temperature is 37.8°C or higher, or sign and symptoms of Fever.

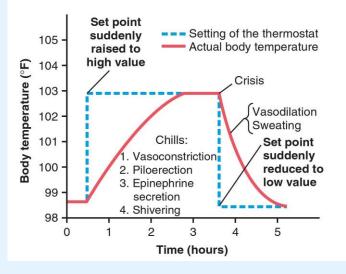
Like feels warm to the touch, or giving a history of feeling feverish, chill or sometimes even cold.

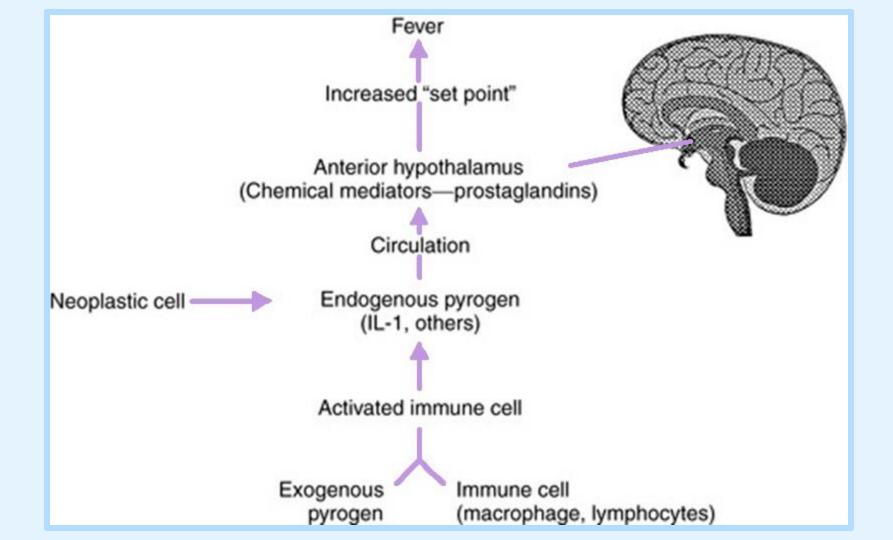




# Fever Physiology, Why Do We Develop Fever Sometimes?

- Body temperature is regulated by the CNS at the level of the hypothalamus.
- The normal body temperature range from 36.1 to 37.2
- Fever is a normal physiologic phenomenon caused by the release of either exogenous or endogenous pyrogens (any substance that causes fever).
- When a fever occurs, the hypothalamic thermoregulatory center shifts its set-point upward.
- This upward shift is due to ↑ prostaglandin E2 (PGE2) in the preoptic area of the hypothalamus (increased PGE2 is caused by circulating pyrogens)





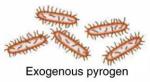
#### Pyrogens

#### Endogenous Pyrogens

The list of currently recognized pyrogenic cytokines includes interleukin-1 (IL-1 [IL-1α and IL-β]), tumor necrosis factor-α (TNF-α), IL-6, ciliary neurotropic factor (CNF), and interferon Activated leukocytes Pyrogenic cytokines (IL-1, TNF-α, IFN-γ) IL-6

#### Exogenous Pyrogens

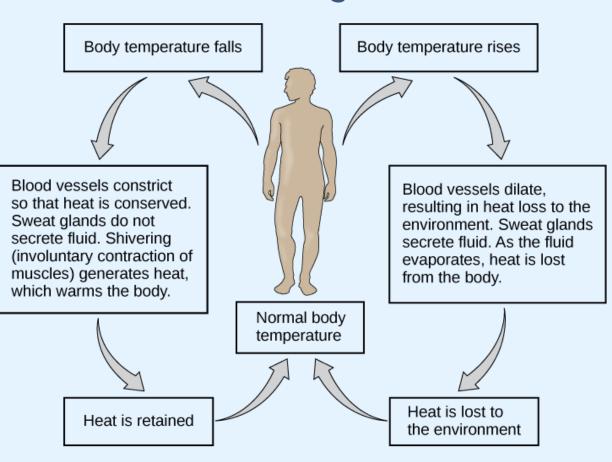
(IFN)



bacterial lipopolysaccharide (LPS) induces fever directly (rather than indirectly through the induction of pyrogenic cytokines) by interacting with Kupffer's cells, thereby initiating pyrogenic signals that are transmitted to the preoptic area of the hypothalamus via the hepatic branch of

the vagus nerve.

# Thermal Regulation



# Fever vs Hyperthermia

Fever occurs when either endogenous or exogenous pyrogens cause an elevation in the body's thermoregulatory set-point.

In hyperthermia, the set-point is unaltered, and the body temperature becomes elevated in an uncontrolled fashion due to exogenous heat exposure or endogenous heat production.

During the rising phase of fever, thermoregulation works to increase body temperature

So, in Fever the body increasing heat production and decreasing heat loss.

During hyperthermia the thermoregulation system works to decrease body temperature

So, in Hyperthermia the body increasing heat loss and decreasing heat production

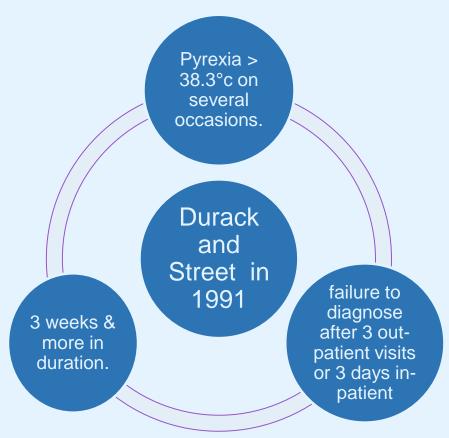
# Fever of Unknown Origin

Pyrexia of unknown origin (PUO) has a differential of >200 diseases.

15–30% of these patients will eventually be given an infective diagnosis (depending on your corner of the globe).

~20% will remain undiagnosed, but in most of these the fever will resolve within 4wks

Oxford: Pyrexia >3 weeks with no identifiable cause after in hospital evaluation for 3 days or >= 3 outpatient visits.



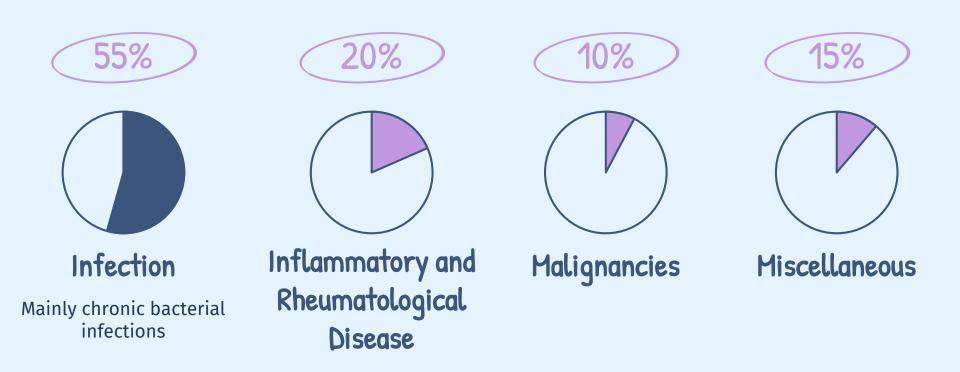
#### The 4 Subtypes of Fever Of Unknown Origin

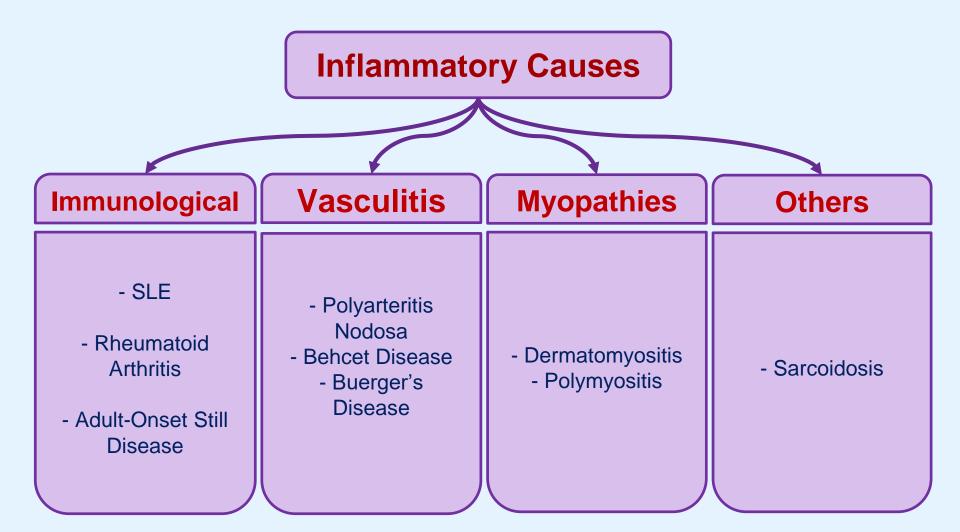
Classic FUO T > 38.3°c (100.9 F) on several occasions. >3 weeks & more in duration. >2 outpatient visits or 3 days in hospital without diagnosis.	<ul> <li>Nosocomial (health care—associated) FUO</li> <li>Fever &gt;38.3°C develops on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest on admission.</li> <li>3 days of investigation and including at least 2 days' incubation of cultures.</li> </ul>
<ul> <li>Neutropenic (immune deficient) FUO</li> <li>Temperature &gt;38.3°C ,Neutrophil count &lt;500/ml , 3 days of investigation .</li> <li>2 days' incubation of cultures (negative cultures after 48 hours) .</li> </ul>	<ul> <li>HIV-associated FUO</li> <li>Fever &gt;38.3°C</li> <li>&gt;3 weeks for outpatients or &gt;3 days for hospitalized patients and appropriate investigations were done over 3 days, including 2 days' incubation of cultures (negative cultures after 48 hours).</li> <li>HIV infection is confirmed</li> </ul>

#### Summary of Definitions and Major Features of the Four Subtypes of Fever of UnknownOrigin (FUO)

CLASSIC FUO	NOSOCOMIAL (HEALTH CARE-ASSOCIATED) FUO	NEUTROPENIC (IMMUNE- DEFICIENT) FUO	HIV-RELATED FUO
>38.3° C (100.9° F), >3 wk, >2 visits or 3 days in hospital	>38.3° C (100.9° F), >3 days, not present or incubating on admission	>38.3° C (100.9° F), >3 days, negative cultures after 48 hr	>38.3° C (100.9° F), >3 wk for outpatients, >3 days for inpatients, HIV infection confirmed
Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Health care–associated infections, postoperative complications, drug fever	Majority due to infections, but cause documented in only 40%-60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, IRIS
Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower limb deep veins	Wounds, drains, devices, sinuses, urine	Skin folds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Months	Weeks	Days	Weeks to months
Weeks	Days	Hours	Days to weeks
	<ul> <li>&gt;38.3° C (100.9° F), &gt;3 wk, &gt;2 visits or 3 days in hospital</li> <li>Community, clinic, or hospital</li> <li>Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia</li> <li>Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder</li> <li>Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower limb deep veins</li> <li>Imaging, biopsies, sedimentation rate, skin tests</li> <li>Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments</li> <li>Months</li> </ul>	CLASSIC FUOCARE-ASSOCIATED) FUO>38.3° C (100.9° F), >3 wk, >2 visits or 3 days in hospital>38.3° C (100.9° F), >3 days, not present or incubating on admissionCommunity, clinic, or hospitalAcute care hospitalCancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermiaHealth care-associated infections, postoperative complications, drug feverTravel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorderOperations and procedures, devices, anatomic considerations, drug treatmentFundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower limb deep veinsWounds, drains, devices, sinuses, urineImaging, biopsies, sedimentation rate, skin testsImaging, bacterial culturesObservation, outpatient temperature chart, investigations, avoidance of empirical drug treatmentsDepends on situationMonthsWeeks	CLASSIC FUOCARE-ASSOCIATED) FUODEFICIENT) FUO>38.3° C (100.9° F), >3 wk, >2 visits or 3 days in hospital>38.3° C (100.9° F), >3 days, not present or incubating on admission>38.3° C (100.9° F), >3 days, negative cultures after 48 hrCommunity, clinic, or hospitalAcute care hospitalHospital or clinicCancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermiaHealth care-associated infections, postoperative complications, drug feverMajority due to infections, but cause documented in only 40%-60%Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorderOperations and procedures, devices, anatomic considerations, drug treatmentStage of chemotherapy, drugs administered, underlying immunosuppressive disorderFundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower limb deep veinsWounds, drains, devices, sinuses, urineSkin folds, IV sites, lungs, perianal areaImaging, biopsies, sedimentation rate, skin testsDepends on situationAntimicrobial treatment protocolsObservation, outpatient temperature chart, investigations, avoidance of empirical drug treatmentsDepends on situationAntimicrobial treatment protocolsMonthsWeeksDays

# Aetiology





# Adult-Onset Still Disease Systemic Onset Juvenile Idiopathic Arthritis

#### Triad:

(1) Daily fever, (2) inflammatory polyarthritis, and a (3) transient salmon-pink maculopapular rash.

#### Epidemiology

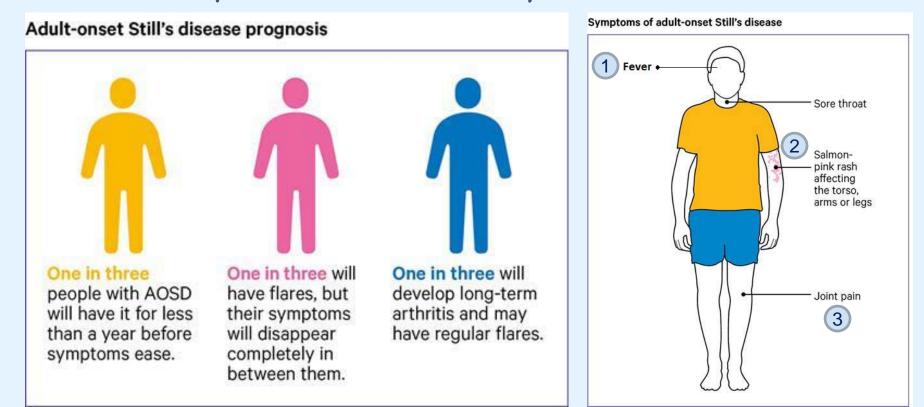
Females > Males. It has a bimodal age of distribution, the first peak between the ages of fifteen to twenty-five and the second between thirty-six to forty-six.

#### Treatment

For Pain: Mild -> NSAIDs, Moderate to Severe -> Glucocorticoids. **DMARDs** 

### Adult-Onset Still Disease

#### Systemic Onset Juvenile Idiopathic Arthritis



# Familial Mediterranean Fever

<u>Autosomal recessive gain of function mutation in IL-1 gene characterized by</u> <u>uncontrolled activation of neutrophils.</u> <u>Brief acute self-limited episodes of fever and polyserositis</u>.

Primarily among ethnic groups of Mediterranean origin, with a carrier rate of 1 in 5 individuals.

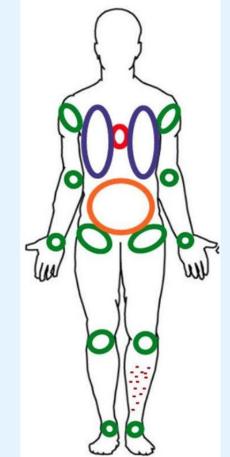
#### **Diagnosis:**

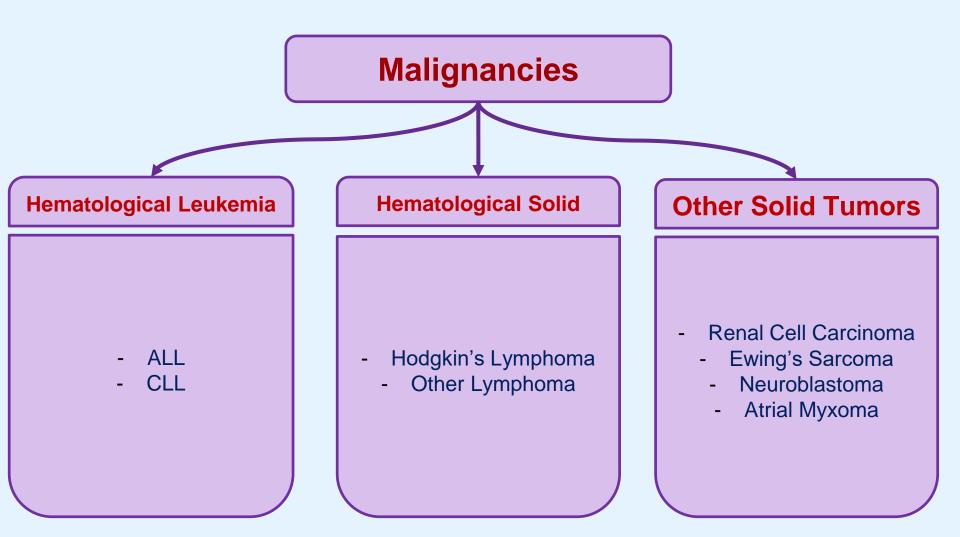
Fever + one more:

- a) Pleuritic chest pain
- b) Sterile peritonitis (Sever abdominal pain)
- c) Arthritis
- d) Rash resembling erysipelas.

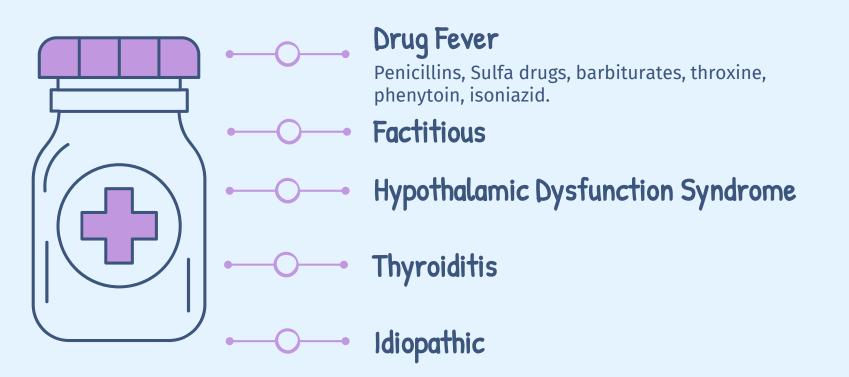
Complications: Amyloidosis and renal failure

Treatment: <u>Colchicine</u>, interrupts neutrophil migration.





### Miscellaneous Causes

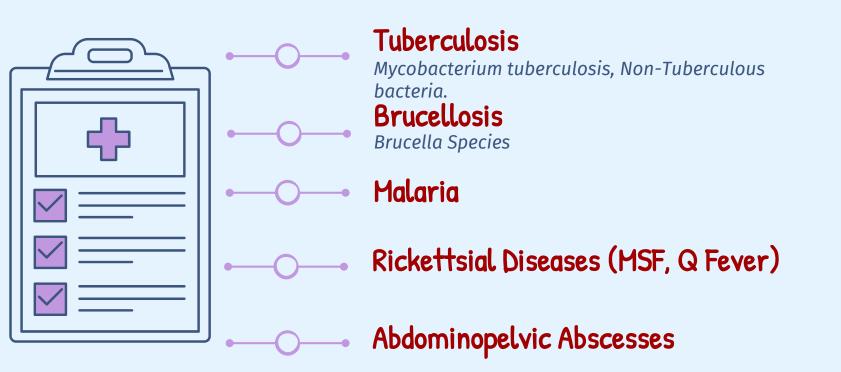


### Infectious Causes

- Tuberculosis (TB)
- •Q fever
- Brucellosis
- HIV infection
- Abdominopelvic abscesses
- Cat scratch disease (CSD)
- Epstein-Barr virus (EBV) infection
- Cytomegalovirus (CMV) infection
- Enteric (typhoid) fever
- Toxoplasmosis
- Extrapulmonary TB

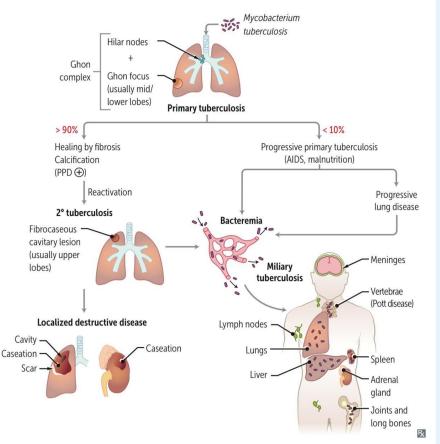
Regional infections:Histoplasmosis Coccidioidomycosis Leptospirosis Visceral leishmaniasis Rat-bite fever Louse-borne relapsing fever

### Infectious Causes



### Mycobacterium tuberculosis

#### **Tuberculosis**



#### Pathogenesis:

Tuberculosis is spread via airborne transmission. It starts in the lower lobes of the lung and creates caseous necrosis. The caseous necrosis in the granuloma of the lower lobe of the lung is called "Ghon focus". The Ghon focus with the calcified hilar lymph node is called "Ghon complex". This is primary TB. During this stage, some bacteria might escape the ghon focus via the blood and go to different organs, and becomes latent there. Reactivation in peripheral organs leads to fever of unknown origin.

#### **Diagnosis:**

(1) PPD (2) Chest X-Ray (3) IGRA

**Treatment:** Prolonged Multidrug Regimens

### Brucellosis

The <u>gram-negative</u> bacteria Brucella melitensis (Goats), Brucella abortus (Cattle), Brucella canis (Dogs), Brucella suis (Pigs)



#### Transmission

Direct contact with animals, eating unpasteurized milk products.

#### Presentation (Triad)

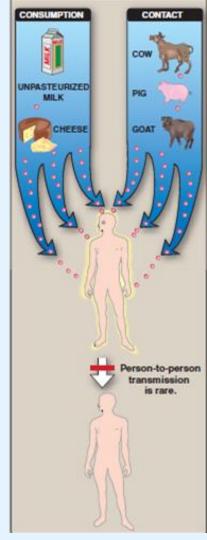
(1) Undulant fever and night sweats.(2) arthralgia (3) Hepatosplenomegaly.

#### Treatment

#### **Brucella** species

• Brucellosis (undulant fever)

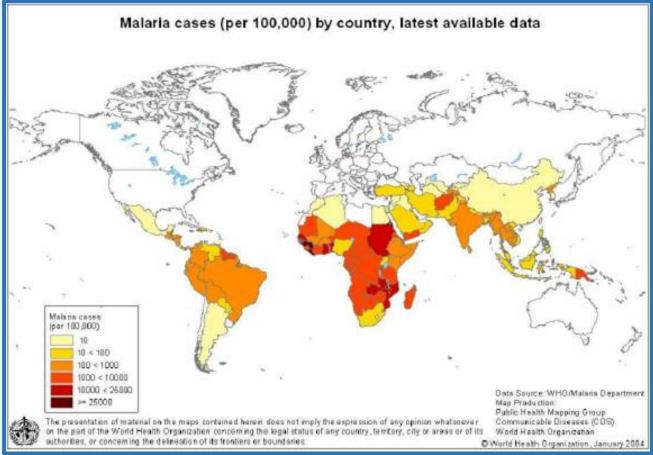


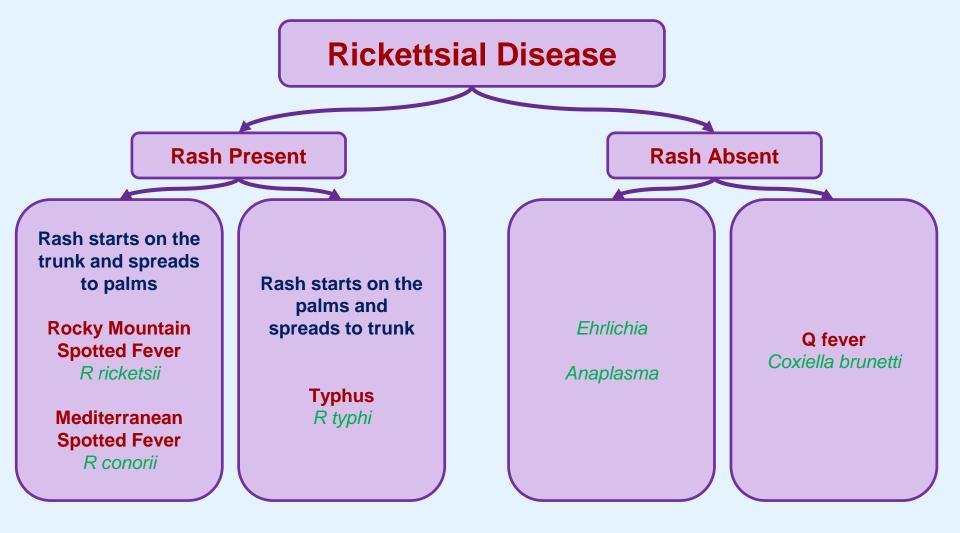


# Malaria

	-			
ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Plasmodium P vivax/ovale P falciparum P malariae	Malaria—fever, headache, anemia, splenomegaly; hypoglycemia in severe disease	Anopheles mosquito	Blood smear: trophozoite ring form within RBC	Antimalarial drugs
O- Plasmodium f Anemi cerebr Plasmodium RBCs occlud capillar	<b>a or</b> <b>Titis</b> m filled de brain	O Other plasm species Fever Jupiter is th biggest plan of them a	ne net	

# Malaria





## Mediterranean Spotted Fever

**Tranmsission**: Goat and the brown dog tick, *Rhipicephalus sanguineus*. **Distribution**: in Mediterranean and black sea countries.

#### **Presentation:**

- 1) Fever
- 2) Maculopapular rash
- 3) Tache noir
- 4) Maculopapular rash that starts on the trunk and spreads to the wrists and ankles, sparing the face.
- 5) Severe disease: pneumonia and myocarditis

**Testing:** PCR testing of lesions, serological testing to confirm diagnosis.

Treatment: Doxycycline







# Patterns of Fever

The pattern of fever may help to determine a diagnosis, although it has limited value in comparison to more specific laboratory tests.



### Patterns of Fever

2nd

4th

6th

Continuous Fever

#### 3rd Intermittent Fever

○Quotidian fever ○Tertian fever ○Quartan fever

#### **Recurrent Fever**

**Remittent Fever** 

ORelapsing feverOPel-ebstein feverOPeriodical fever

5th Bi

1st

#### **Biphasic Fever**

Undulant Fever



### Continuous Fever

Course	Temperature permanently over 38°C; daily fluctuations < 1°C.	40°C 24 hours 39°C
	Viral and bacterial infections (e.g.,	38°C
Associated diseases	typhoid fever, lobar pneumonia),	37°C
	Kawasaki disease	36°C

### **Remittent Fever**

Course	Temperature permanently over 38°C; daily fluctuations ≥ 1°C.	40°C 24 hours 39°C
Associated diseases	Viral infections, acute bacterial endocarditis	38°C

## Intermittent Fever

Course	High spike and rapid defervescence	40°C A 24 hours
Associated diseases	Pyogenic/focal infection, TB, juvenile idiopathic arthritis, infective endocarditis, malaria, leptospira, borrelia, schistosomiasis, lymphoma	38°C

# Types of Intermittent Fever

	Course	Example	Illustration
Quotidian fever	With a periodicity of 24 hours	Plasmodium falciparum	Temp (°C) 37 Hours 0 2'4 4'8 7'2 9'6 1'20 1'44 1'68 Days 0 1 2 3 4 5 6 7
Tertian fever	With a 48 hour periodicity	Plasmodium vivax or Plasmodium ovale	Temp (°C) 37 Hours 0 24 48 72 96 120 144 168 Days 0 1 2 3 4 5 6 7
Quartan fever	With a 72 hour periodicity	Plasmodium malariae	Temp (°C) 37 Hours ô 2'4 4'8 7'2 9'6 1'20 1'44 1'68 Days 0 1 2 3 4 5 6 7

### **Recurrent Fever**

	Course	Example
Relapsing 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 relapsing fever and louse-borne relapsing fever
Pel-Ebstein fever	Fever lasting 1–2 weeks followed by an afebrile period of 1–2 weeks	Hodgkin lymphoma
Periodical fever	Fever that recurs over months or years in the absence of associated viral or bacterial infection or malignancy	Periodic fever syndromes (e.g., familial Mediterranean fever, hyper- IgD syndrome)

# Biphasic Fever

Course	A fever that breaks and returns once more	40°C 24 hours
Associated diseases	Dengue fever, leptospirosis	38°C

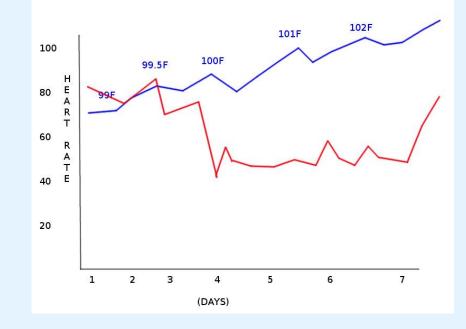
## Undulant Fever

Course	Temperature rises gradually and falls (like a wave) over days to weeks.	40°C 24 hours
Associated diseases	Brucellosis	38°C

# Faget Sign

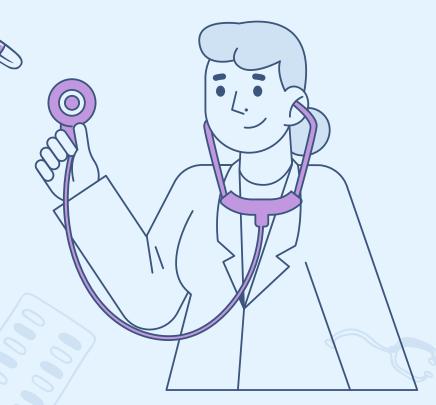
#### **Pulse-temperature dissociation**

The presence of both fever and relative bradycardia. Can be caused by many infectious diseases, including yellow fever, typhoid fever, dengue fever, ebola virus disease, brucellosis, tularemia, and Legionella infection.









# Approach to Fever of Unknown Origin







#### 1. Patient profile:

Age?

Gender?

Adress?

#### **2. HOPI:**

Details about the fever:

How was it measured? Highest vs lowest grade? Documented or not?



# History

- <u>**Onset**</u> ( acute vs insidious?) Sinusitis , TB , Malignancy
- <u>Grade (</u> low grade vs high grade) TB , Malaria
- **<u>Duration</u>** ( short duration vs long duration )- Malaria , brucillosis
- <u>Progression</u> (decreasing, worsening, cyclical or constant)
- <u>Timing</u> (Continuous, Remittent, Intermittent... explained above) (day vs night)
- <u>Responding to medications?</u>
- <u>Risk factors</u> (diet, milk , raw eggs, drugs, allergy, contact with infected person)





# History

#### **Associated symptoms:**

DETAILS about any associated symptom

#### **Review of systems:**

General: chills and rigors , sweating , loss of weight (TB/malignancy) , trauma

-RS: cough, sputum, sore throat, nasal congestion

-GI: diarrhea, abdominal distension, pain and blood in stool (shigella), loss appetite

-UTI: frequency, dysuria, haematuria.

-MSS: myalagia , lower limb pain (DVT) , skin infection , arthritis( joint swelling ,pain) , malar rash

-CNS :convulsions (Meningitis / Brain tumor) ,activity and sleep patterns

-ENT: ear discharge and otalgia (otitis media).

# History

**Past medical history:** Previous episodes? Admissions? Chronic diseases? Autoimmune diseases? Drugs?

Past surgical history: When was it? Any complications?

Social history: Smoking? Travel history? Pets?

Family history: Similar complaints? Genetic background?

## Physical Examination



If in distress, if patient appears toxic

Step 2 Vital Signs

> Level of tachycardia

Hemodynamic Instability (low blood pressure, arrhythmias) Step 3 Document the Fever

> Cintinuous? Goes back to normal? Recurrent?

## Physical Examination

### Step 4: Search for a diagnostic clue!

- Skin: Rashes, skin folds, IV sites, wounds, drains.
- Hands and nails: Splinter hemorrhages
- Head: Fundoscopic changes, oropharynx, temporal arteritis, ear.
- Neck: Lymph node enlargement, thyroid.
- Respiratory: Rate, wheeze
- Cardiac: New/changing cardiac murmurs.
- Abdomen: Tenderness or rigidity, hepatosplenomegaly.
- Lower limb: DVT.
- Neurological (especially meningism signs).
- Musculoskeletal: Signs of arthritis.

# Investigations

### Minimal Diagnostic Workup

#### Laboratory studies:

- CBC with differential
- Acute phase reactants : erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Liver chemistries
- Serum electrolytes
- LDH
- Creatine kinase
- Urinalysis and urine culture Blood culture (three sets) if bacteremia is suspected

#### Imaging

- X-ray or CT chest
- Ultrasound or CT abdomen and pelvis

Targeted testing based on diagnostic clues?

# Investigations

### Additional Nonspecific Laboratory Studies

- Serum ferritin: Highly elevated levels are suggestive of a noninfectious etiology.
- Cryoglobulins: may be positive in patients with neoplastic disease, inflammatory disease, or viral infection
- <u>- Cold agglutinins</u>: elevated in certain infections (e.g., mycoplasma pneumonia, EBV, viral hepatitis), malignancy (e.g., lymphoma), or inflammatory disease
- Uric acid: elevated levels are suggestive of malignancy
- Further serologic testing, e.g., for EBV infection, CMV infection, brucellosis, bartonellosis

# Investigations

## Advanced Imaging Studies

- FDG-PET scan : Consider for all patients without a diagnosis after initial diagnostics, especially those with elevated CRP and/or ESR.

- CT or MRI chest and abdomen: Consider if not already obtained, FDG-PET is unavailable, or FDG-PET indicates an intrathoracic or intraabdominal abnormality.

- Transesophageal echocardiogram (TEE): Consider for suspected bacterial endocarditis.

#### Invasive tests

- Lymph node biopsy: Consider for patients with lymphadenopathy.
- **Temporal artery biopsy:** Consider in patients  $\geq$  55 years of age.
- Liver biopsy: Consider in patients with suspected hepatic involvement
- **Bone marrow studies:** if diagnostic clues for myeloproliferative or myelodysplastic disease are present (e.g., pancytopenia, atypical cells on peripheral blood smear).
- **Consider bone marrow culture** for suspected culture-negative bacterial endocarditis, miliary tuberculosis, or typhoid fever if it would alter the management.
- **Diagnostic laparoscopy or laparotomy:** rarely indicated unless a biopsy cannot be obtained using another modality

## Treatment and Management

 Unless a patient is clinically unstable, do not use empiric therapy in cases of FUO; patients are usually stable. Treatment is directed toward the underlying etiology once discovered. The diagnostic evaluation in up to 25% of patients with FUO fails to identify a cause; however, these patients have a good prognosis. If the initial workup is negative and the fever persists, repeat the same workup in several months.

 Avoid empiric therapy (e.g., antibiotics, glucocorticoids) unless there is rapid clinical deterioration, neutropenic fever or if a life-threatening etiology is suspected.

• Avoid antipyretics if feasible.

# Management

## Why Shouldn't We Give Empiric Therapy?

- Rarely specific
- Underlying disease may remit spontaneously (false impression of success).
- Disease may respond partially and this may lead to delay in specific diagnosis.
- Side effect of the drugs can be misleading.

# Specific Therapy for Different Causes

### Inflammatory Causes

FMF	Colchicine
Adult-onset still disease	<ul> <li>Nonpharmacological: e.g., smoking cessation.</li> <li>Pharmacological:         <ul> <li>Mild: NSAIDs</li> <li>Severse: DMARDs</li> </ul> </li> </ul>

## Specific Therapy for Different Causes Infectious Causes

<ul> <li>Vancomycin or ampicillin + Gentamicin, may be used.</li> </ul>
doxycycline PLUS rifampin
Antimalarial drugs
<ul><li>Doxycycline</li><li>Chloramphenicol (pregnant patients)</li></ul>

# Specific Therapy for Different Causes

#### Neutropenic Fever

Empirical broad-spectrum antimicrobial therapy is commenced when cultures have been obtained. The most common regimens for neutropenic fever are broadspectrum penicillins, e.g. piperacillin-tazobactam. The routine addition of aminoglycosides to these agents is not supported by trial data. If fever has not resolved after 3-5 days, empirical antifungal therapy (e.g. caspofungin) is added.







# THANK YOU



