

FEVER OF UNKNOWN ORIGIN

FUO

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DEFINITION

Fever: higher than **38**(100.4 F)(**38,3**) on several occasions

Duration: > **3 weeks**

INPATIENTS:

Failure to reach a diagnosis despite **3-7 days in hospital**

Despite intelligent invasive investigation

OUTPATIENTS

after **3 outpatient visits.**

One week of intelligent invasive investigation

FUO IS OFTEN A diagnostic **DILEMMA**

30-51% of patients remain **undiagnosed** after extensive evaluation

They generally have a **favorable outcome**

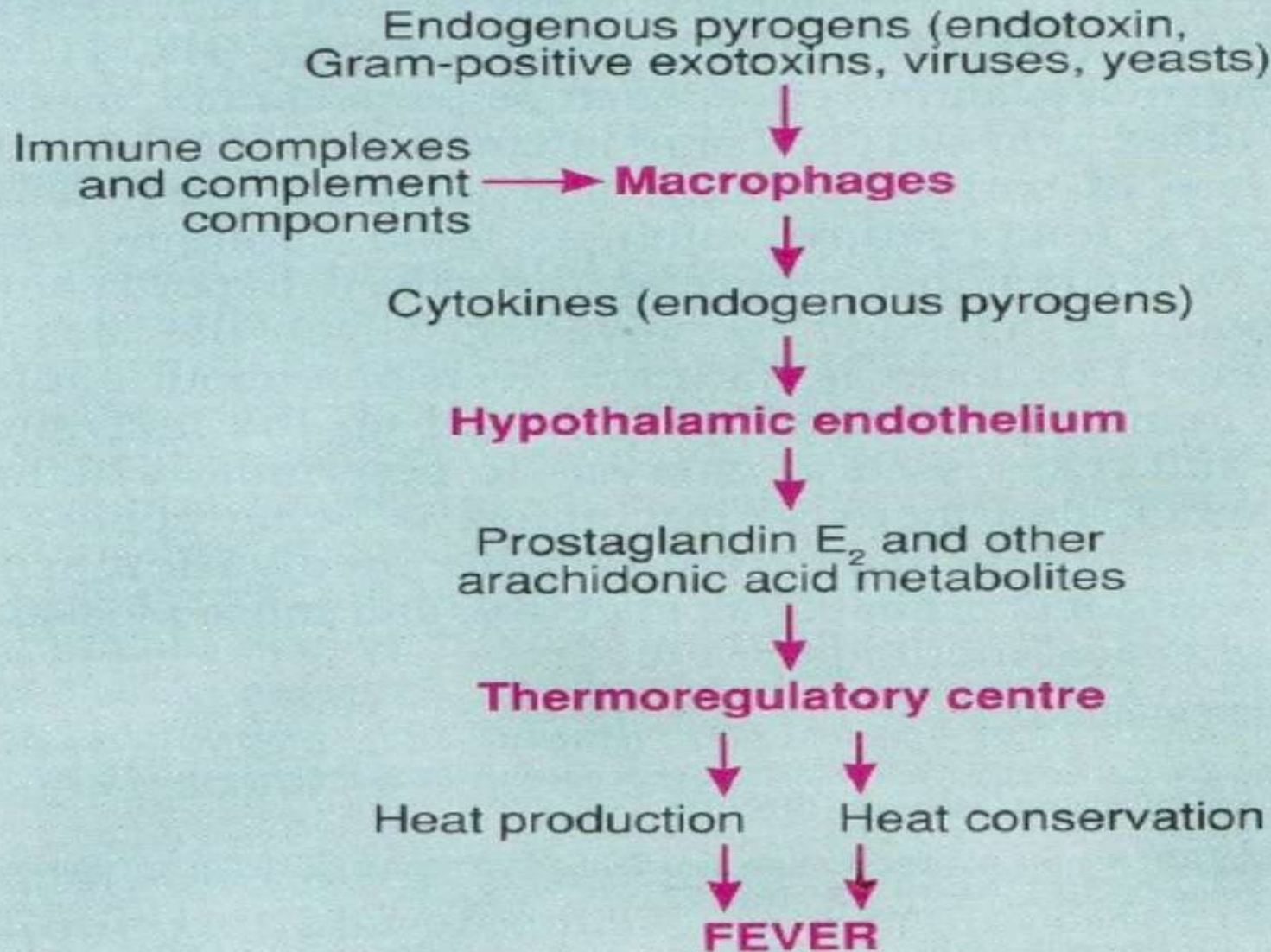
The **fever** usually **resolves** after 4-5 weeks .

have **good prognosis**

NORMAL BODY TEMPERATURE

- The hypothalamus is the heat-regulating center of the body
- The normal body temperature ranges from 37.0 degree C and 37.5 degree C
- Evening temperatures being 0.5 degree C higher than in the morning.
- Rectal temperature > oral temperature (0.4 degree C)
> axillary temperature (1 degree C)

Pathogenesis of fever



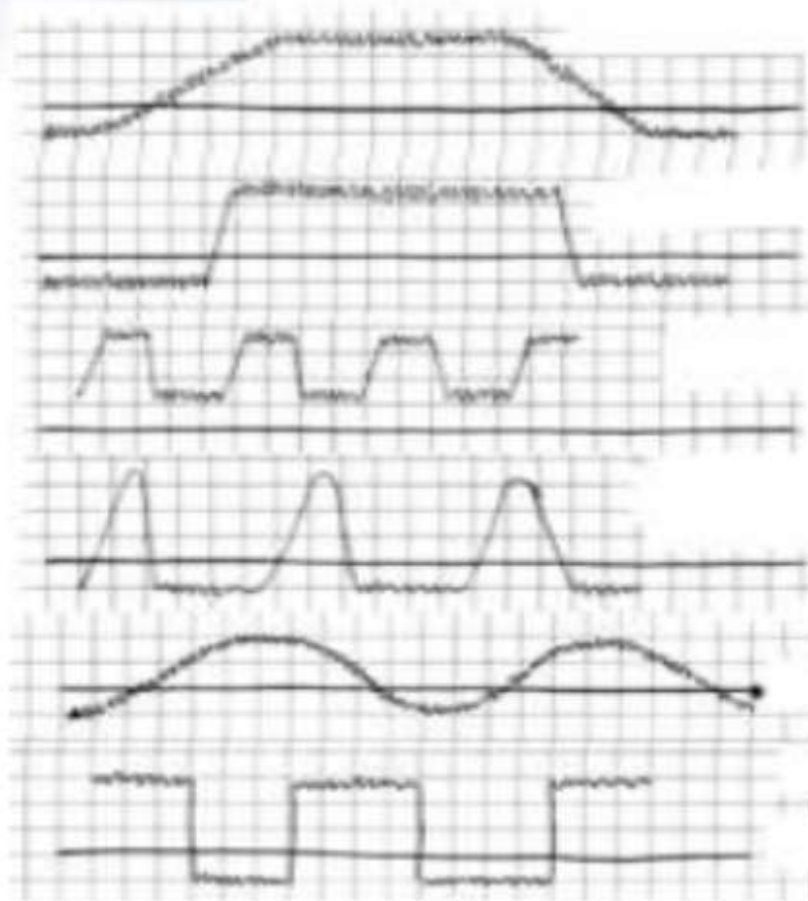
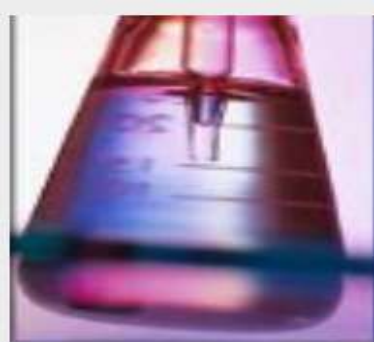


Type of fever (fever patterns)

- **Intermittent fever** - Fever that touches normal for a few hours during the day. It is seen in malaria, acute pyelonephritis, local boils and furuncles.
- **Remittent fever** - Fever that fluctuates more than 1.5 degree F in 24 hours without touching normal.
- **Continuous fever** - Fever that does not touch normal and fluctuates less than 1.5 degree F in a day. It is seen in enteric fever, Bacterial endocarditis, viral pneumonia.

متناوبة

متقطعة



A

B

C

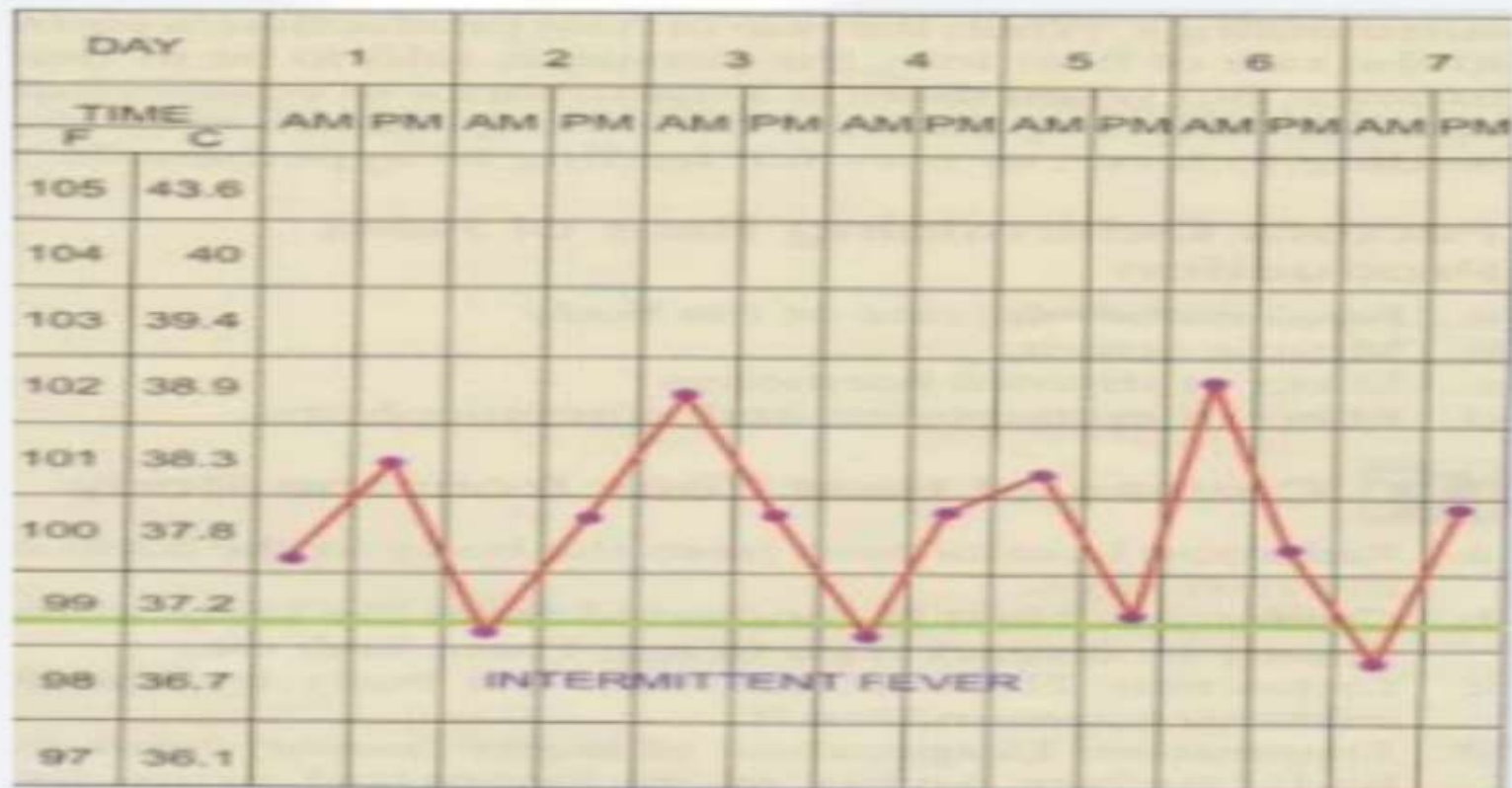
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E

F

- A&B-Continuous fever
- C-Remittent
- D-Intermittent
- E-Relapsing fever
- F-Undulant fever

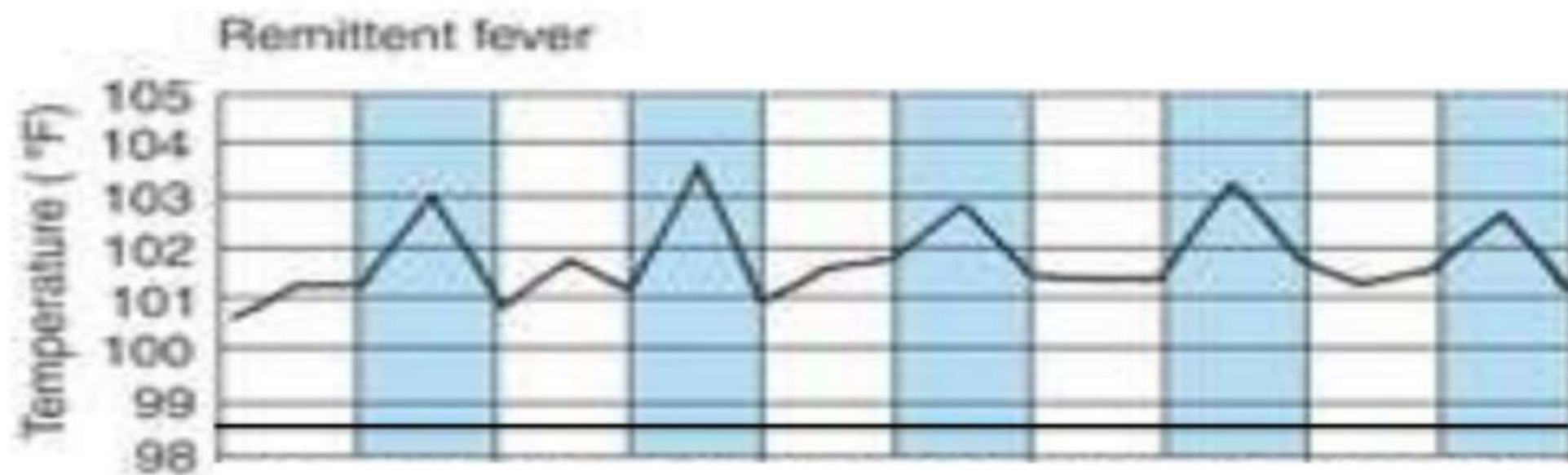
Intermittent fever



E.g, malaria, kala-azar, septicaemia, pyaemia

Remittent fever - Fever that fluctuates by more than 1.5 degree F but never touches the baseline in 24 hours

- Seen in infective endocarditis



Continuous fever.




- Eg. Lobar pneumonia, infective endocarditis, enteric fever.

- Types of intermittent fever :
 - Quotidian fever, with a periodicity of 24 hours, typical of *Plasmodium falciparum*
 - Tertian fever, with a 48 hour periodicity, typical of *Plasmodium vivax* or *Plasmodium ovale*
 - Quartan fever, with a 72 hour periodicity, typical of *Plasmodium malariae*

Pel-ebstein fever - Fever lasting for 3-10 days followed by an afebrile period of 3-10 days

- Seen in hodgkins lymphoma



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- ✓ Periodic fever- fever syndromes with regular periodicity, e.g. cyclic neutropenia, PFAPA, familial Mediterranean fever.

Evaluation a patient with fever

History :

- Family Hx, Inherited and Congenital Diseases (FMF ?)
- Surgical Hx,(Abscesses?)
- Immunization status,(Aids ?)
- Occupational Hx,(Lead ?)
- Travel Hx,(Aids ?, Tropical diseases ?).
- Nutrition Hx, (Milk?)
- Drug Hx,(Penicillins? Vancomycin , Nsaids ?, Ranitidine ?)
- Sexual Hx,(Sex related diseases?)
- Animal contact. (cows , dogs , cats?)

Evaluation a patient with fever

Physical Examination

Documentation of fever and exclusion of factitious fever.

Measure the fever more than once in the presence of the nurse.

Pay special attention to the eyes (fundoscopic changes) , skin (rashes), lymph node , heart (murmurs) , abdomen and genitalia.

Pulse- temperature relationship (**Liebermeister's rule** : the pulse rise about 15 b/min for each degree centigrade of fever).

The pattern of fever (**continuous, remittent, intermittent**)

Common causes

Infections		Malignancies	Systemic inflammatory d.	Miscellaneous
Abscesses (especially intra-abdominal)	Kala azar (visceral leishmaniasis)*	Aleukemic leukemia	Allergic granulomatous angiitis	Disorders of temperature regulation (neurologic and dermatologic)
African tick bite fever*	Kikuchi's disease	Atrial myxoma	Antiphospholipid syndrome	Drug fever ^Δ
Amebic liver abscess *	Lassa fever*	Colon cancer	Behçet's disease	Environmental (metal and polymer fume fevers)
Anaplasmosis/ehrlichiosis*	Leptospirosis*	Hepatocellular carcinoma	Cryoglobulinemia	Factitious fever
Babesiosis*	Lyme disease*	Liver meta.	Giant cell arteritis	Familial Mediterranean F.
Brucellosis *	Osteomyelitis	Kaposi's sarcoma	Granulomatosis with polyangiitis (formerly Wegener's disease)	Inflammatory bowel d.
Castleman's disease	Prostatitis	Leukemia	Granulomatous hepatitis	Neuroleptic malignant syndrome
Bacterial endocarditis	Pyelonephritis	Lung cancer	Hypersensitivity vasculitis	Periodic fever
Chronic active hepatitis	Pyometria	Lymphomas especially non-Hodgkin's	Inflammatory bowel disease	Pulmonary emboli
Culture-negative endocarditis*	Q fever*	Multiple myeloma	Parotitis	Retroperitoneal hematomas
Cytomegalovirus	Relapsing fever (Borrelia recurrentis)*	Myelodysplastic syndromes	Polyarteritis nodosa	Systemic exertion intolerance disease (chronic fatigue syndrome)
Dental abscesses	Rheumatic fever	Renal cell car.	Reactive arthritis (formerly Reiter's syndrome)	Thyroiditis
Dengue*	Sinusitis	Sarcoma	Sarcoidosis	
Diskitis	Toxoplasmosis		Still's disease	
Epididymitis	Typhoid fever *		S.LUPUS ERYTH.	
Fascioliasis*	Tuberculosis		Takayasu's arteritis	
Filariasis*	Whipple's disease			
Gonococcal arthritis	Zika virus*			
Herpes simplex encephalitis				
Infectious mononeucleosis				

COMMON CAUSES OF FUO

Infections (16%) : tuberculosis ,abscesses,b. endocarditis,osteomyelitis.

Malignancies (7%) : Lymphoma (non-Hodgkin), Leukemia, Renal cell car , HCC.

Connective tissue disease (22%): adult still disease , giant cell arteritis .

Miscellaneous (4%)

Drugs (4%): Eosinophilia and Rash are present **only in 25% of cases** .

- Sulfa, **Penicillins**, Nitrofurantoin, **Vancomycin**, Antimalarials (Nivaquin).
- H1-**H2** Antihistamine.
- Barbiturates , Phenytoin.
- **NSAID**, Antithyroid drugs, Hydralazine, methyldopa

No diagnosis (51%) good prognosis

TUBERCULOSIS (TB)

pulmonary tuberculosis, and the **CRX** is normal in **15 to 30%** of cases.

in patients with **AIDS** is often **subtle**

skin test is positive in fewer than **50%** of patients with TB.

The interferon-gamma release assay also has low sensitivity in active TB .

Sputum samples are positive in only **25%** of cases.

Techniques for isolation of *Mycobacterium tuberculosis* from blood include isolator **cultures** and polymerase chain reaction (PCR) on BACTEC blood culture bottles with evidence of early growth .Both of these methods have yielded positive results in approximately **16 days**, although PCR may be more sensitive and specific .

ABSCESSSES

Predisposing diseases :

cirrhosis, steroid , diabetes. recent surgery. immunosuppressive medications.

Intraabdominal occult abscesses:

can develop in subphrenic, omental, pouch of Douglas, pelvic, and retroperitoneal locations in addition to visceral sites.

Perinephric or renal abscesses: may be caused by urinary tract infection
urine cultures may be negative (40%).
30% normal urin .

ABSCESSSES

Pyogenic liver abscesses usually follow **biliary tract** disease or abdominal suppuration such as **appendicitis** or **diverticulitis**.

Amebic liver abscesses :

cannot be distinguished on clinical grounds from **pyogenic abscesses**.

amebic serology is **positive** in more than **95%** of cases **acute** or **previous**
negative anti-amebic antibody exclude!.

Splenic abscess:

Endocarditis is the most common infection associated with splenic abscess.

Hematogenous seeding rather than contiguous spread accounts for the majority of **splenic abscesses**, which are often missed prior to **autopsy** .

Bacterial endocarditis

Lack of murmurs.

administration of antimicrobials may obscure the detection of bacteremia.

Echocardiography (Transesophageal) :

positive in over 90% of cases of infective endocarditis presenting as FUO

False-positive due to anatomic abnormalities or noninfective vegetations.

false-negative due to small vegetations or those that have already embolized.

Endocarditis in intravenous drug users is often right sided .

Connective tissue diseases

Adult Still's disease:

quotidian (daily) fevers, arthritis, and an evanescent rash.
similar to systemic juvenile idiopathic arthritis in children.

Giant cell arteritis:

15% of cases of fuo in older adults(>50 years).

headache, abrupt loss of vision, symptoms of polymyalgia rheumatica ,
anemia, and a high ESR , Jaw claudication.

Temporal artery biopsy is suggested in all cases of suspected GCA.

Other :

polyarteritis nodosa , Takayasu's arteritis (which is common in Japan),
granulomatosis with polyangiitis (Wegener's), and mixed cryoglobulinemia.

Malignancy

Lymphoma, especially **non-Hodgkin's**

Leukemia and Myelodysplastic syndromes occasionally present with fever .

Renal cell carcinoma presents with fever in approximately 20 percent of cases.

Hepatocellular carcinoma or other tumors metastatic to the liver

Atrial myxomas are uncommon but present with fever in approximately one-third of cases. Other findings include arthralgias, emboli, and hypergammaglobulinemia. The diagnosis is usually established by **echocardiography**.

Less common causes

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Herpes simplex encephalitis				
Infectious mononeucleosis				

Workup

CBC , ESR,CRP, ALT, AST, TB, LDH,RF,CPK,WIDAL,WRIGHT. Electrolytes.

ANA, **P-ELECTROPH**, FT4. Urin.

If liver tests are abnormal, **hepatitis A, B, and C** serologies.

Tuberculosis tests:PPD(purified protein derivative),

IGRA(interferon gamma release assay) **or tuberculin skin test**

Cultures: blood cultures for aerobic and anaerobic

in cases in which antibiotics are indicated, all blood cultures should be obtained **before administering antibiotics** .

Urine culture (including microscopic examination, and urine culture)

Sputum and **Stool** cultures (in the presence of pulmonary or GI Sx)

CXR, Echo, (CT) or (MRI) of the **chest, abdomen, and pelvis**.

BIOPSY

Liver biopsy :

granulomatous hepatitis : Miliary TB , Brucellosis , Sarcoidosis .

Lymph node biopsy:

Lymphoma

Temporal artery biopsy :

giant cell arteritis , polyarteritis nodosa .

Pleural or pericardial biopsy :

extrapulmonary TB.

Bone marrow biopsy :

Leukemia , MM . .

Therapeutic trials

Empiric antibiotics :

can suppress but cure an infection process such as **ABSCESS**
TB therapeutic trial (Rifampicin) may suppress but not cure
Staphylococcal Osteomyelitis or Endocarditis

Glucocorticoids may suppress but not cure **SARCOIDOSIS , VASCULITIS**

Before use a careful evaluation for infection should precede such a trial .

NAPROXEN therapeutic trial :

rapid decrease of fever of malignancy , specially lymphoma
But lesser decrease of fever of infection !

و شكرا لإصفائكم

Thank you



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