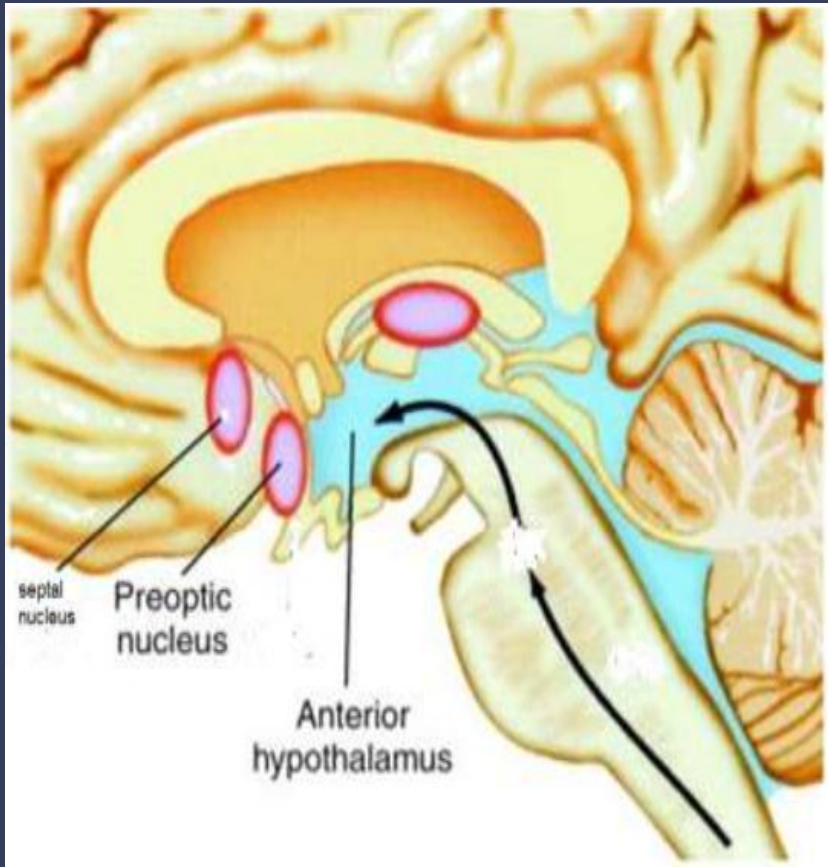
fever of unknown origin

objective

- Proper definition of FUO.
- Epidemiology.
- Etiology.
- Approach to the patient with FUO.
- Treatment strategies.

Fever is a protective response to infection . An elevated temperature enhances the body’s innate defense mechanisms by making conditions less favorable
for infectious microorganisms to thrive.



- Normal body temperature is maintained by a complex regulatory system in the anteroir hypothalamus,preoptic area,temperature sensitive area,thermal set point .

Pyrogens(Substances mediate the elevation of core body temperature).

Exogenous pyrogens derived from outside the host ,like Microorganisms and their products and, toxins.

They induce release of (endogenouse pyrogens) from macrophages.

Pyrogen (cytokines)trigger hypothalamus to release PGE2 resulting in Resetting of thermostatic temperature,activation of vasomotor center ,vasodilatation and heat production.

defintion

- Fever higher than 38.3ºC on several occasions.
- Duration of fever for at least three weeks .
- Uncertain diagnosis after one week of study in the hospital

- **Establishing that a patient has an FUO As noted above, the degree and duration of fever are not the only criteria for defining an FUO.**
- **Prior to concluding that a patient has an FUO, the following evaluation should have been performed and should have been unrevealing:**

History and Physical examination.

- Complete blood count, including .
- differential and platelet count.
- Routine blood chemistries, including liver enzymes and bilirubin .

- Hepatitis serology (if liver tests abnormal).
- Urinalysis, including microscopic examination, and urine culture.
- Chest radiograph

Epidemiology

- **The incidence of specific etiologic agents of FUO varies by.**
- **age of the population.**
- **potential exposure to infectious agents.**
- **host susceptibility to infection.**

Etiology

- Three general categories of illness account for the majority of "classic" FUO cases .

1. Infections.
2. Malignancies .
3. systemic inflammation (ctd).

Other causes

- Factious fever.
- Drug induced.
    1. Carbamazepine
    2. Isoniazid
    3. Nitrofurantoin
    4. Lamotrigine
    5. Penicillin
    6. Phenytoin

Distribution of different diagnoses

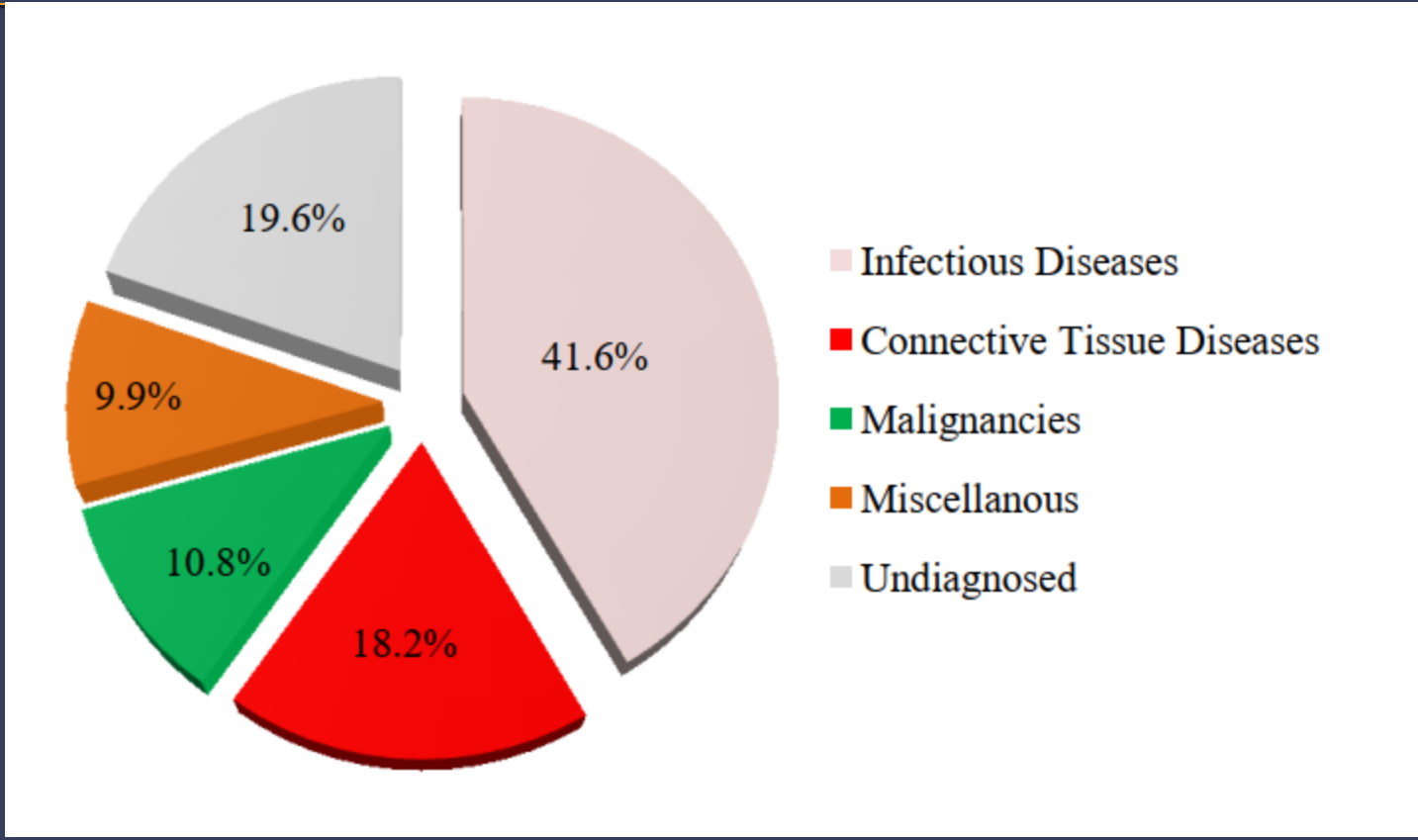


Table 1: Summary of recent studies on PUO patients performed in 2000 2017

Study	Country	Year of study	Population	Total cases	Etiological cause %				
					Infectious Diseases	Inflammatory	Malignancies	Miscellaneous	Undiagnosed
Mansueto[13]	Italy	1991–2002	Adult	91	32.0	12.0	14.0	10.0	32.0
Zenone[14]	France	1999–2005	Adult	144	23.0	26.0	10.0	15.0	26.0
Hot[15]	France	1999 2005	Adult	280	11.0	27.0	20.0	9.0	33.0
Efstathiou[9]	Greece	2001 2007	Adult	111	30.0	33.0	11.0	5.0	21.0
Bleeker-Rovers[10]	Netherland	2003 2005	Adult	73	16.0	22.0	7.0	4.0	51.0
Vanderschueren[16]	Belgium	2000–2010	Adult	436	17.0	24.0	11.0	10.0	39.0
Kucukardali[35]	Turkey	2003–2004	Adult	154	34.0	34.0	14.0	5.0	16.0
Montasser[46]	Egypt	2015	Adult	374	66.3	7.2	7.2	11.5	7.8

Viral infections

Most viruses cause self-limited infections of brief duration.

cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis viruses can cause FUO.

Symptoms and signs of these infections can be nonspecific.

Liver enzymes may be elevated. Viral cultures, serologic studies, and molecular techniques such as polymerase chain reaction (PCR) can be used to facilitate the Dx.

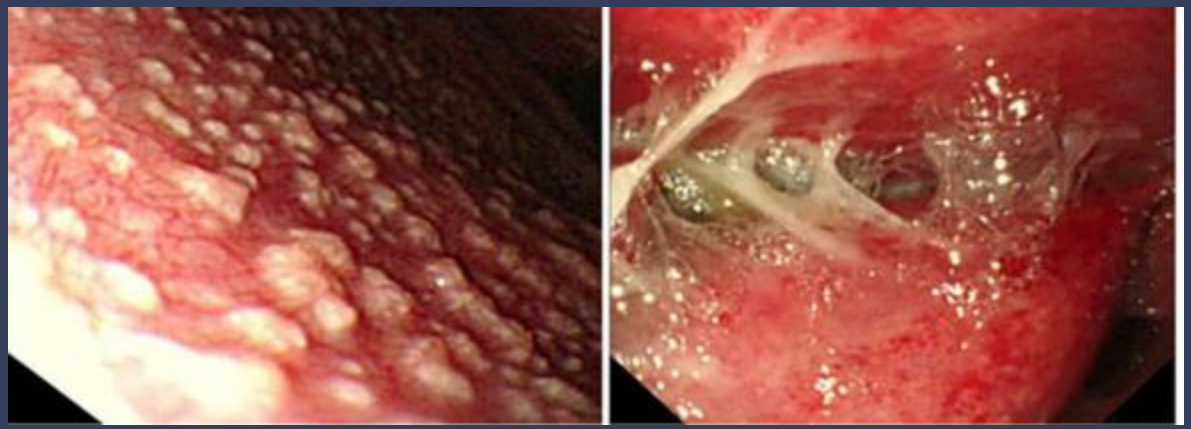
Brucellosis

Brucellosis frequently is considered in the differential diagnosis of FUO because the infection can be present as chronic non specfic symptoms and signs.

so, it is important to ask about exposure to animals or animal products.

Tuberculosis (TB)

Tuberculosis (important cause of FUO) Extrapulmonary TB (disseminated TB, or TB of the liver, peritoneum, pericardium, or genitourinary tract), is more likely to cause FUO than pulmonary TB, which is usually evident on chest radiography



Salmonellosis

Salmonella species can cause typhoidal as well as localized gastrointestinal (GI) illness

The diagnosis can be made with blood and stool cultures, which should be repeated if initially negative and fevers persist.

Toxoplasmosis

It should be considered in patient with exposure to soil contaminated with feline (cats) feces.

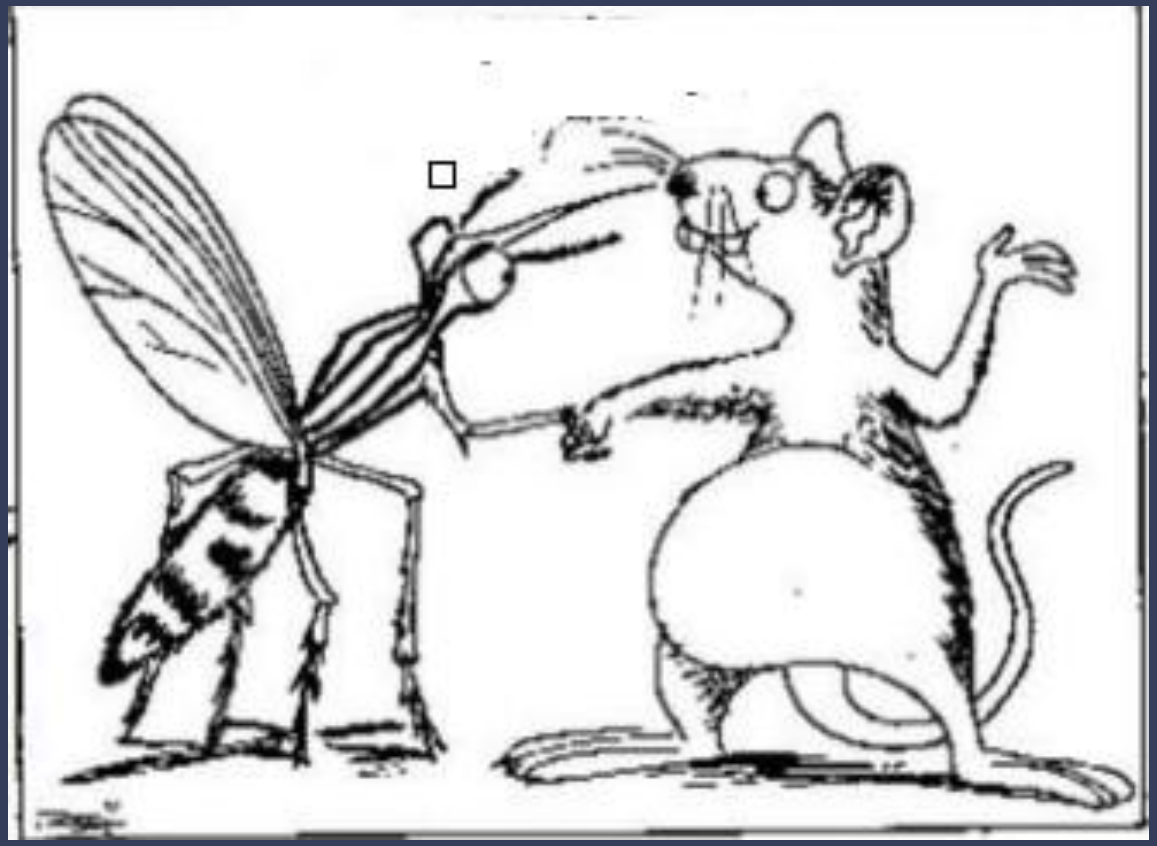
A rise in antibody titer can establish the diagnosis; however, a single high antibody titer is not sufficient.

Leptospirosis

Leptospirosis is a common zoonotic infection with worldwide distribution.

The clinical manifestations are nonspecific and may include fever, rigors, myalgias, headache, cough, and gastrointestinal complaints.

Leptospirosis typically occurs after exposure to environmental sources, such as animal urine, contaminated soil or water (particularly during swimming), or infected animal tissue.

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MALAWI
ZAMBIA
MOZAMBIQUE
ZIMBABWE
NAMIBIA
BOTSWANA
SWAZILAND
LESOTHO
SOUTH AFRICA
Malaria-endemic countries
Endemic country
Non-endemic country

Malaria

Malaria is an important consideration in a patient with FUO.. Although the patient frequently has a history of travel to areas where malaria is endemic.

Malaria infection can be delayed for months after travel . Splenomegaly usually accompanies fever The diagnosis is made by examining appropriately stained thin or thick smears of blood.

Localized infection

When common localized infections cause FUO, they may have an unusual presentation.

Careful and repeated history and physical examination, and careful review and interpretation of laboratory tests, can help to diagnose these infections.

approach

- The most critical feature of the evaluation of a patient with FUO is to take a careful history and to reassess the patient frequently.
- It is important to look for uncommon presentations of common diseases and to perform a detailed physical examination .

History of Presenting Illness (HOPI)

1. Onset
   - - acute: Malaria, pyogenic infection
   - - gradual: TB, thyphoid fever

2. Character
   - high grade fever: UTI, TB, malaria, drug
3. Pattern
   - sustained/persistent: Thyphoid fever, drugs

- intermittent fever:
  - Daily spikes: Abscess, TB, Schistosomiasis
  - Twice-daily spikes: Leishmaniasis
- -relapsing/ recurrent fever: Non-falciparum malaria, Brucellosis, Hodgkin's lymphoma

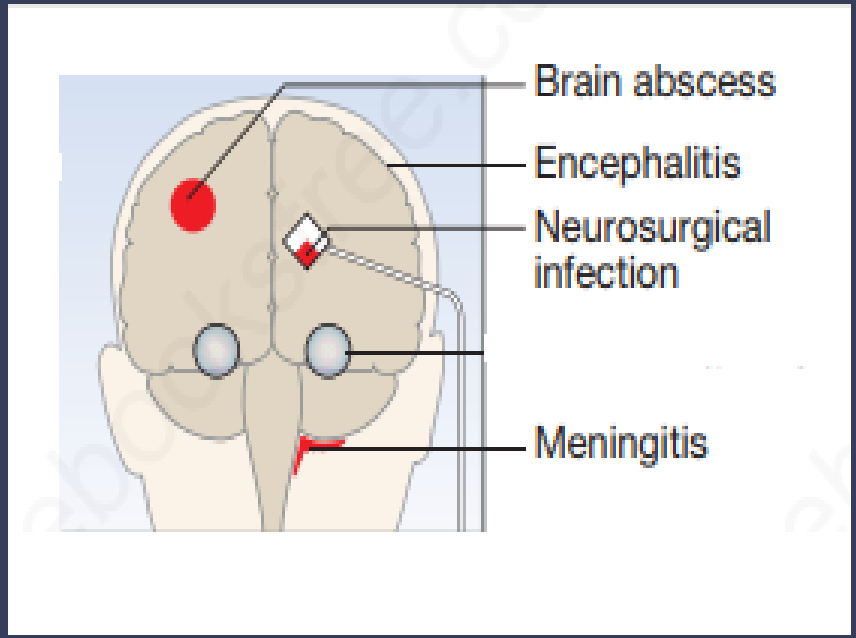
5。 Associated symptoms

- Chills & rigors
  - bacterial, rickettsial and protozoal disease,
  - influenza, lymphoma, leukaemia, drug-induced
- Night sweats
  - TB, Hodgkin's lymphoma
- Loss of weight
  - Malignancy, TB
- Cough and Dyspnoea
  - Miliary TB, multiple pulmonary emboli, AIDS patient with PCP, CMV.
- Headache
  - Giant cell arteritis, typhoid fever, sinusitis

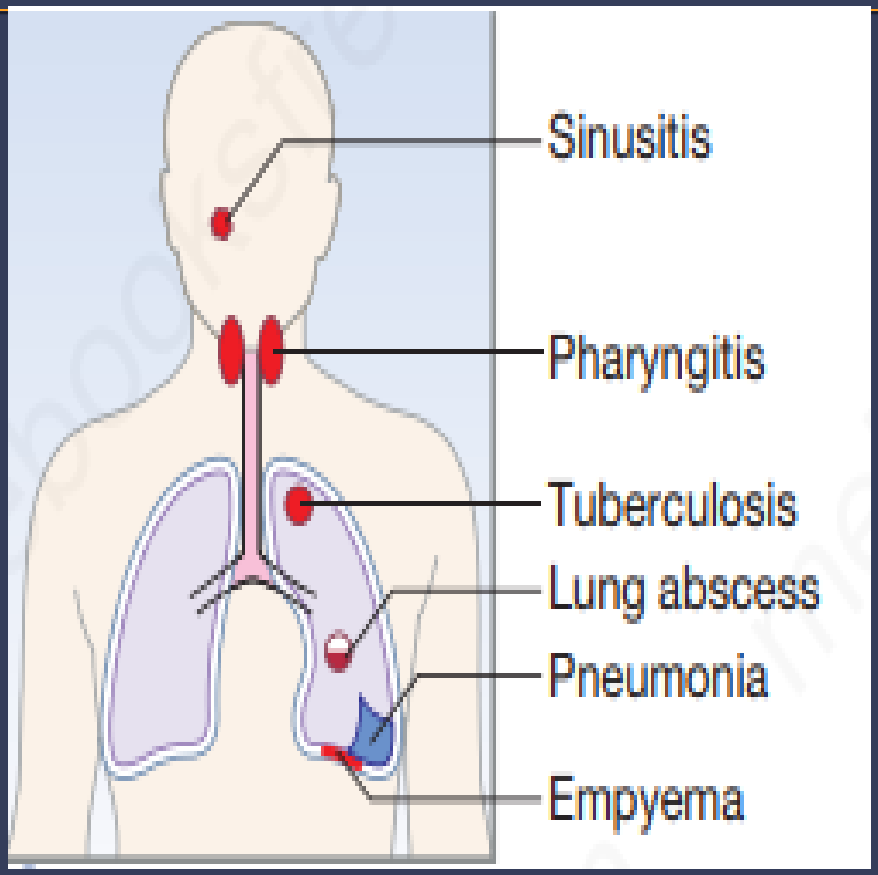
History and physical examination.

- **Detailed review of systems.**
- **Localizing symptoms eg Joint pain RA, SLE, vasculitis**

- Headache +_abnormal behaviour eg mennigitis+_
- encephalitis



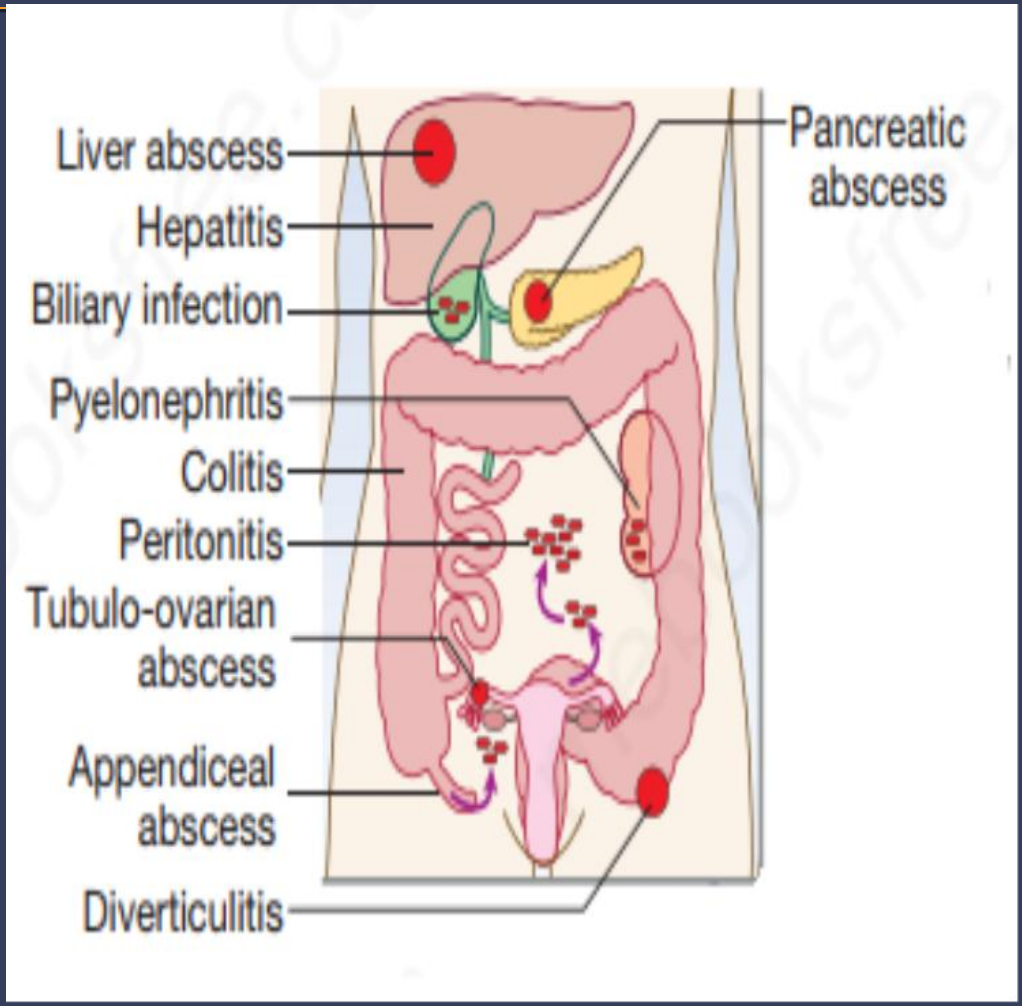
- Resp ROS
- Sorethroat: IM, retropharyngeal abscess, post-Streptococcal infection.



Cvs

- Rh fever endocarditis ,PE

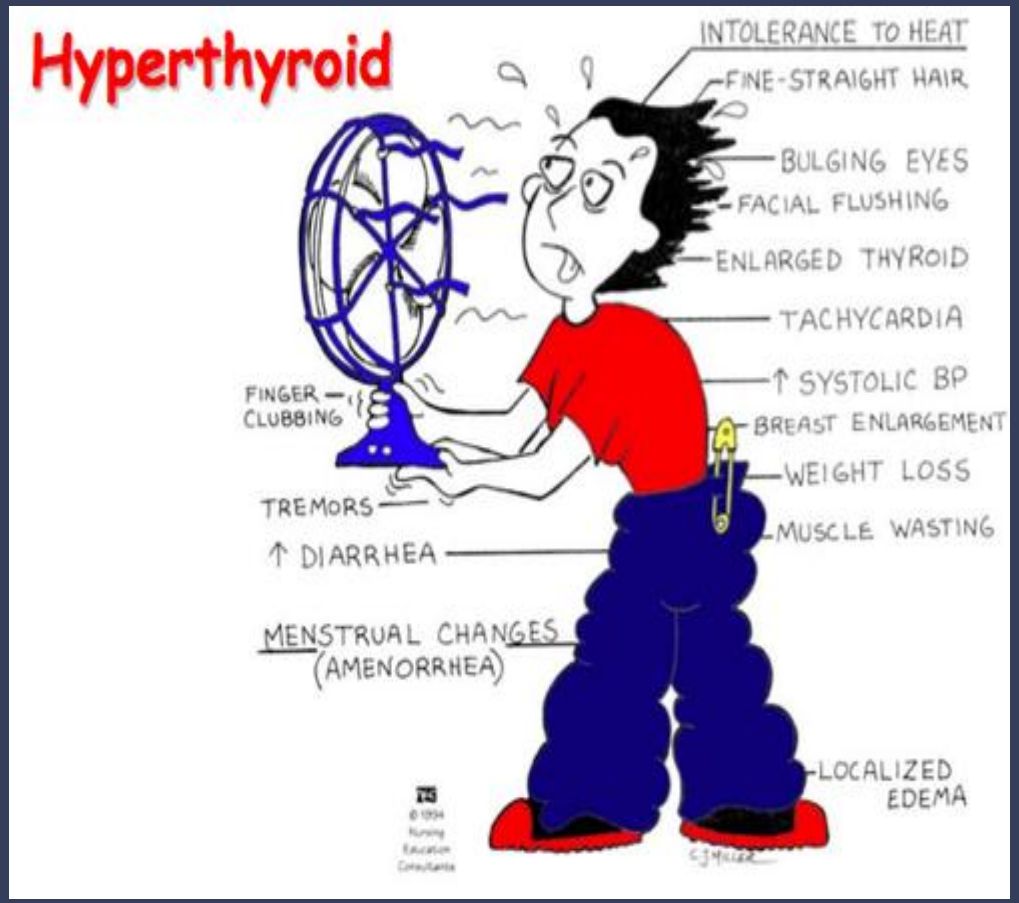
- Abd. Pain and change bowel habbit e g Cholangitis, Crohn’s disease,typhhoid gynaecological infection.



- Bone pain: Osteomyelitis, leukemia.

Endocrine

- thyrotoxicosis



- Skin rash: viral ,CTD

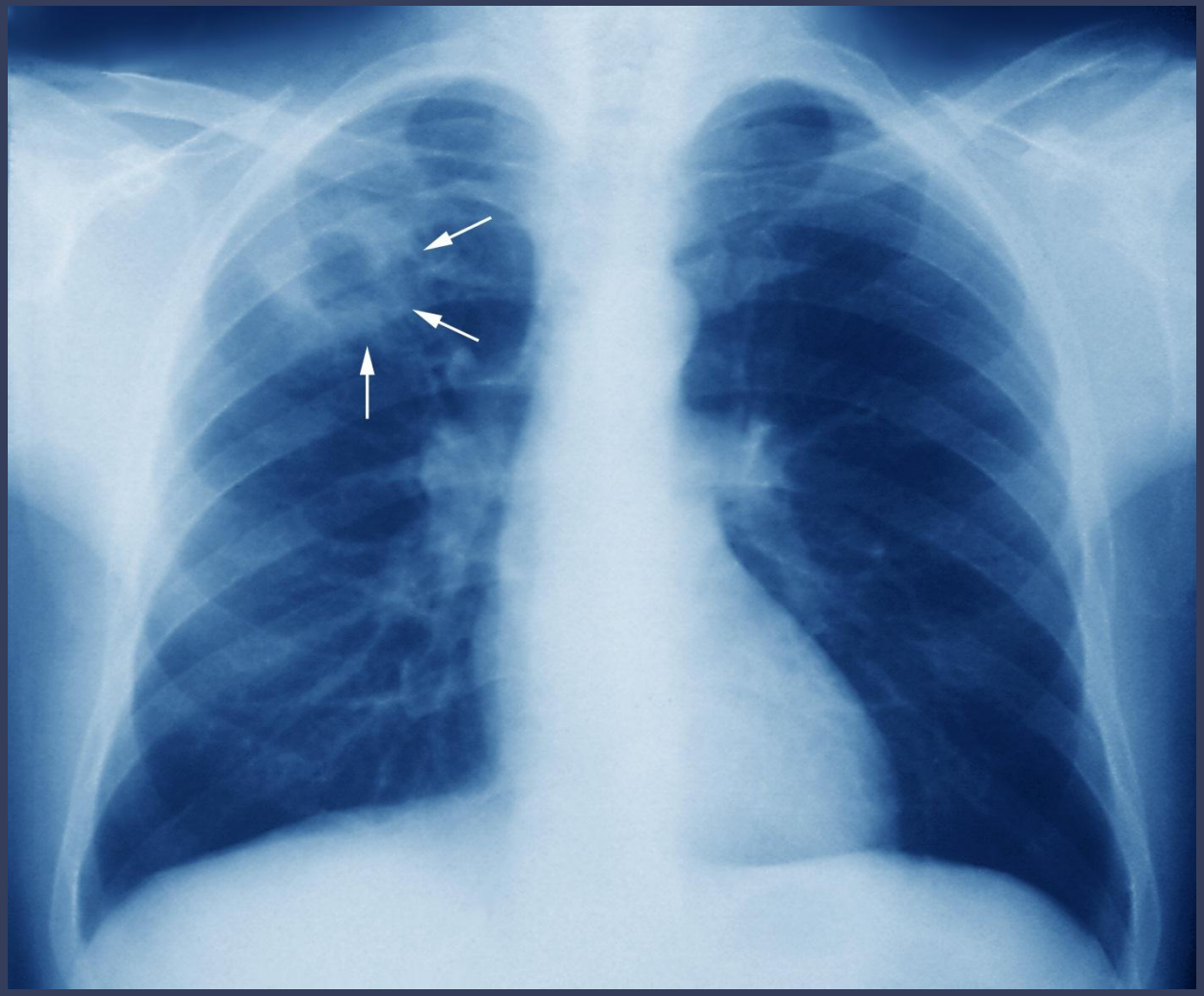
- Travel
- Animal exposure (eg, pets, occupational, living on a farm).recent procedure (dntal,u cathetrization.iv catheters iv drugs
- Immunosuppression.Vaccination.
- Drug history: including antimicrobials.

Lab tests

Stage 1: screening

1. **CBC,. ESR & CRP**
2. **RFT AND LFTs**
3. **Blood culture.cosider bl film for malaria.**
4. **Serum virology .**
5. **Urinalysis and culture**
6. **9. Stool occult blood**
7. **CXR and Tuberculin test**

Lung tb



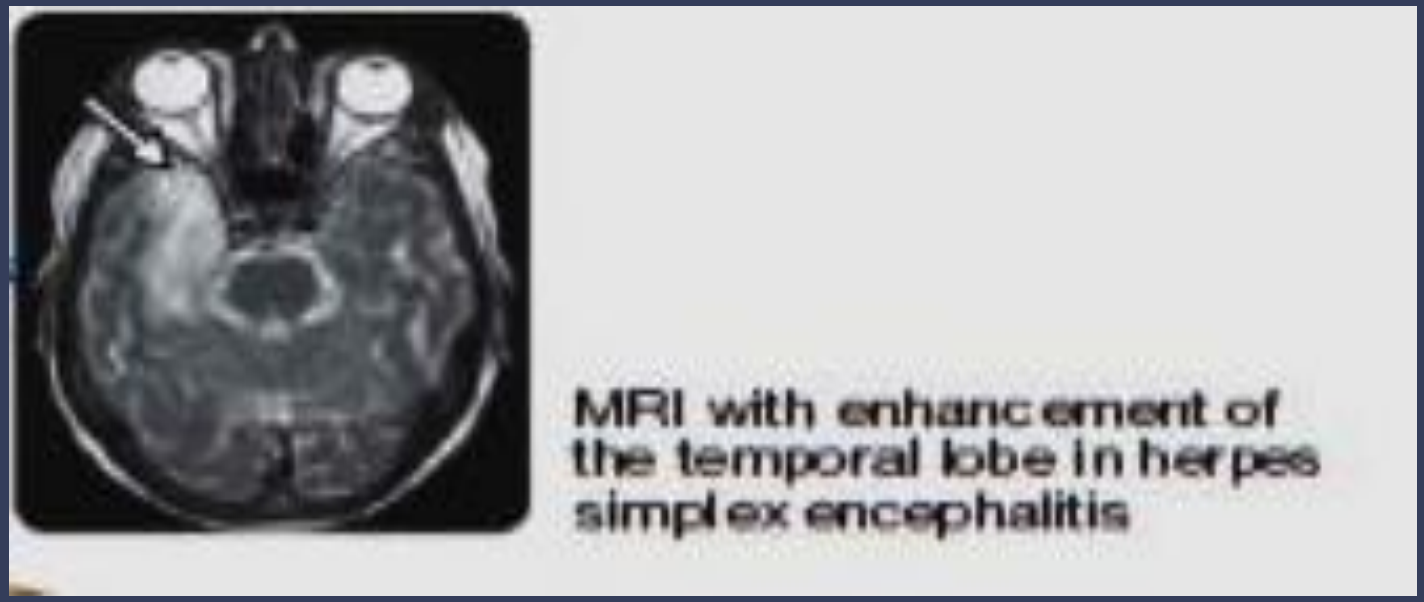
Blood culture

- Three routine blood cultures drawn from different sites over a period of at least several hours without administering antibiotics, if not already performed.
- Aerobic and non aerobic media should be used.

Stage 2

After Repeat history and examination

1. CT (chest,abdomen, pelvis)
2. Autoantibodyscreen(ANA, RF, antidsDNA)
3. LP
4.echocardiography.


MRI with enhancement of
the temporal lobe in herpes
simplex encephalitis

Stage 3

- Tissue biopsy
- Lymph nodes ,bone marrow,liver biopsy.
- Consultation.

Biopsy

- Bone marrow or liver biopsy in the work-up for miliary tuberculosis Liver biopsy for possible granulomatous hepatitis or sarcoidosis.
- Lymph node biopsy for malignancy, especially lymphoma, or infections such as cat-scratch disease.

- Temporal artery to look for giant cell arteritis or biopsy of an affected tissue to diagnose a vasculitic process such as polyarteritis nodosa.

- Pleural or pericardial biopsy in the evaluation of extrapulmonary tuberculosis

Therapeutic trials.

- A therapeutic trial of corticosteroids for an inflammatory process .
- A careful evaluation for infection should precede such a trial.

Antimicrobial agents.

- **Antimicrobial agents could be expected to suppress, but not cure, an infectious process such as an occult abscess since adjunctive drainage would usually be required.**

FUO patients who remain undiagnosed after extensive evaluation generally have a **favorable outcome** and the fever usually resolves after 4-5 weeks.

- Thank u