

Infectious Diseases

Lesson 1

THE FEBRILE PATIENT

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Objectives and learning goal

Objectives

- To study the clinical significance of increased body temperature
- To know the concept of fever of undetermined origin

Learning goal

To achieve enough theoretical information for an initial clinical assessment of a patient who presents with fever

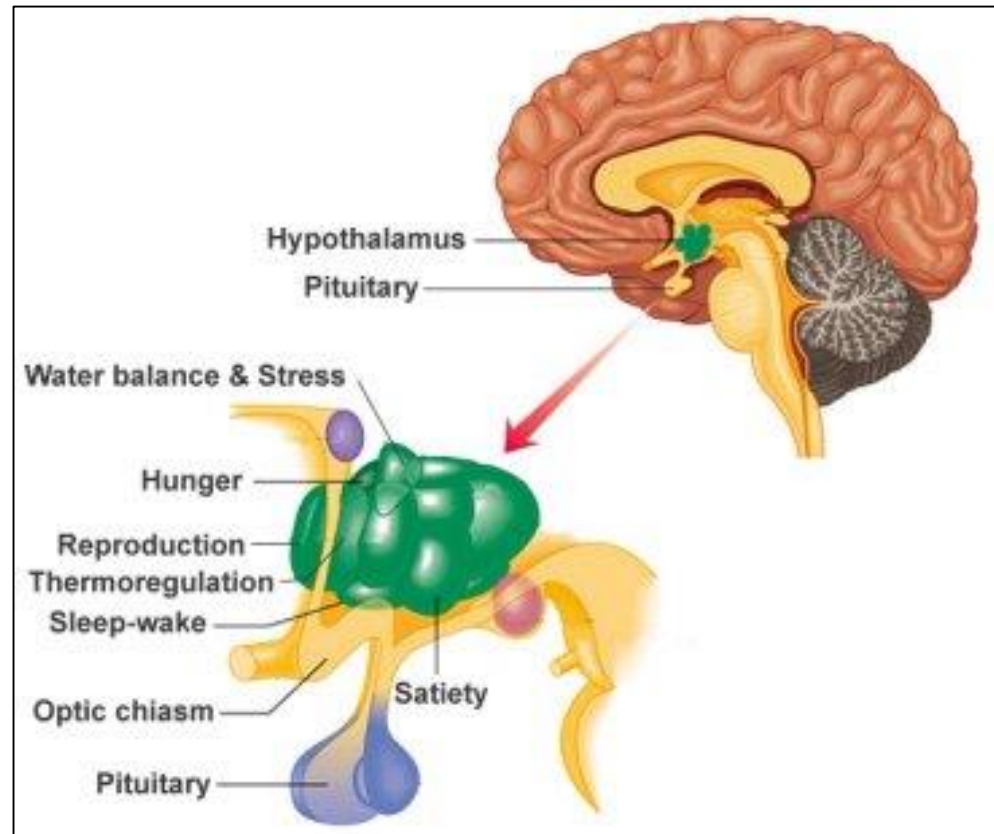
Contents

- Normal temperature and fever
- New onset fever in the hospitalized patient
- Fever of undetermined origin (FUO)
- Diagnostic workup of FUO
- Key messages
- Further reading

Normal temperature and fever

Anatomy of body temperature regulation

- Anterior hypothalamus, region close to the optic chiasm
- Other neural structures, including
 - Brain stem
 - Spinal cord
 - Sympathetic ganglia



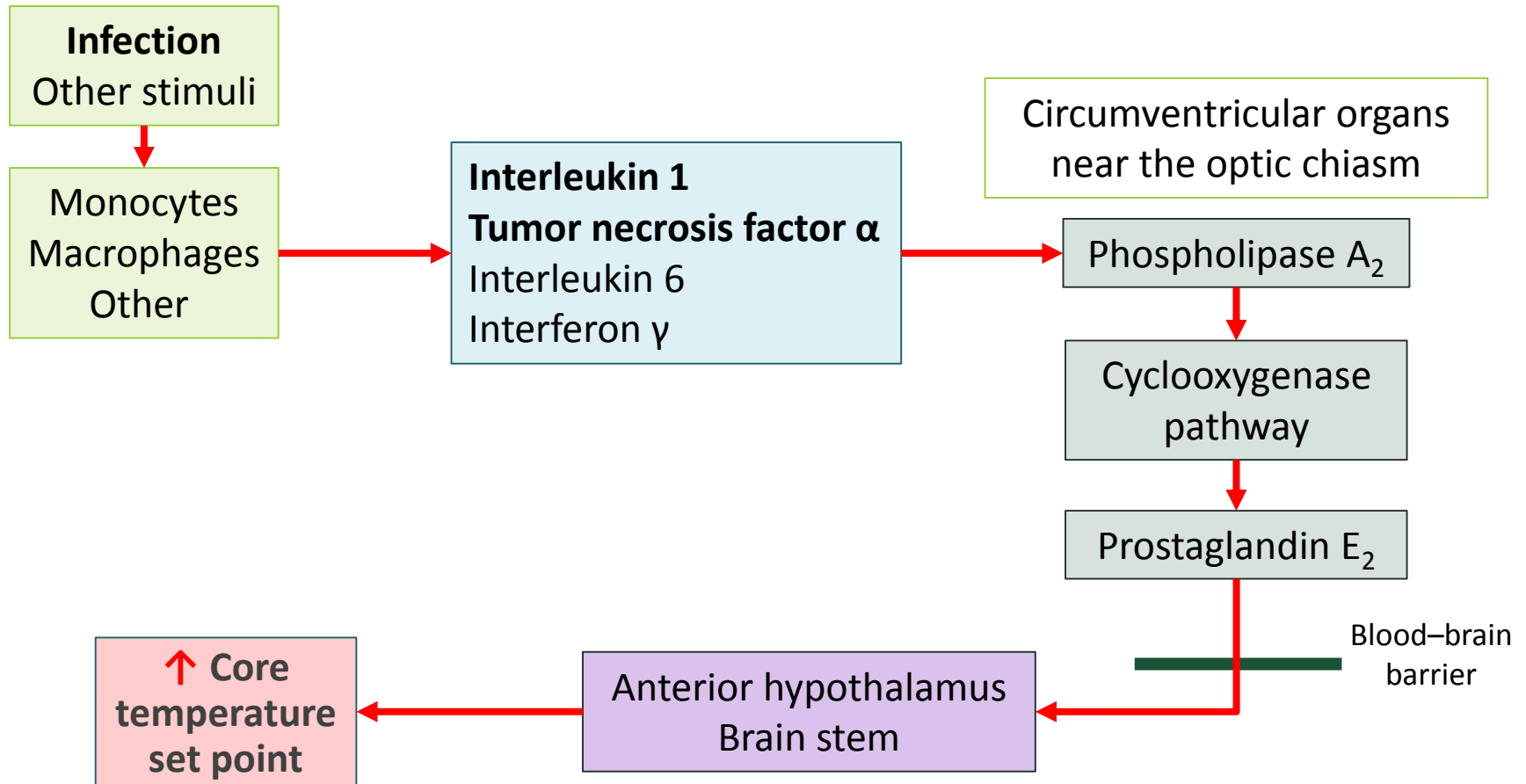
Mechanisms of temperature regulation

- A distinct temperature **set point** is established
- When the body's core temperature drops below that set point, the nervous system →
 - → increases body metabolism
 - → stimulates shivering and chills
- When core temperature exceeds that set point, the nervous system →
 - → increases peripheral blood flow
 - → sweating occurs

Normal body temperature

- 37 °C (= 98.6 °F)
- Varies from individual to individual, i. e., the **set point** may be lower or higher than 37 °C
- Each individual's core temperature varies during the day, being lower in the morning and increasing in the evening
- Before concluding that a patient has a fever, the two previous circumstances must be taken into account

Mechanisms of the febrile response



Benefits of fever

- **Warning** sign for the onset of infection or other disease
- Growth of some viruses, bacteria, fungi, and parasites are **inhibited** by a rise in temperature above 37 °C
- **Enhances** the ability of macrophages and neutrophils to kill foreign pathogens
- Improves cell-mediated **immune** function

Harmful effects of fever

- Patients with heart disease may suffer **cardiac ischemia** because of increase in heart rate and oxygen demands
- Patients with severe **pulmonary** disease may similarly be unable to cope with the increased oxygen demands
- Elderly patients with limited mental capacity may develop **confusion** and **lethargy**
- Children may suffer febrile **seizures**

Treatment of fever - I

- Controversial
- Clearly indicated only in patients who may suffer harmful effects
- The most important is treating the **underlying cause**
- **Acetaminophen**, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs, (all ↓ prostaglandin E₂ and ↓ temperature set point), on a **regular schedule**

Treatment of fever - II

- Direct **cooling** of the body (ice, cold water, etc.):
 - Secondary role
 - Only with drugs that reset the thermal set point, otherwise CNS → chills and shivering → discomfort
- Acetaminophen, high dose, to be avoided in patients with serious underlying liver disease
- Acetylsalicylic acid generally to be avoided in:
 - Children, risk of **Reye's syndrome** (fatal hepatic and renal failure)
 - Patients with coronary heart disease, risk of coronary artery vasoconstriction

Common causes of fever in the general population

- Respiratory tract infections
- Gastrointestinal infections
- Urinary tract infections

New onset fever in
the hospitalized
patient

General considerations

- A very common clinical problem
- Causes are myriad
- Patients frequently have several medical and surgical conditions at a time
- Patients may be severely ill
- A complete present and past medical history and physical exam are key to determine the cause

Postoperative patient

- Wound infection (purulent discharge, erythema, edema, and tenderness) must first be excluded
- **Immediate** postoperative period (24-48 hours), *Streptococcus pyogenes*, severe bacteremia and septic shock, with minimal purulence at the wound
- **Later** postoperative period, *Staphylococcus aureus*, including MRSA, and nosocomial pathogens such as *Pseudomonas* spp., *Klebsiella* spp., and *Escherichia coli*

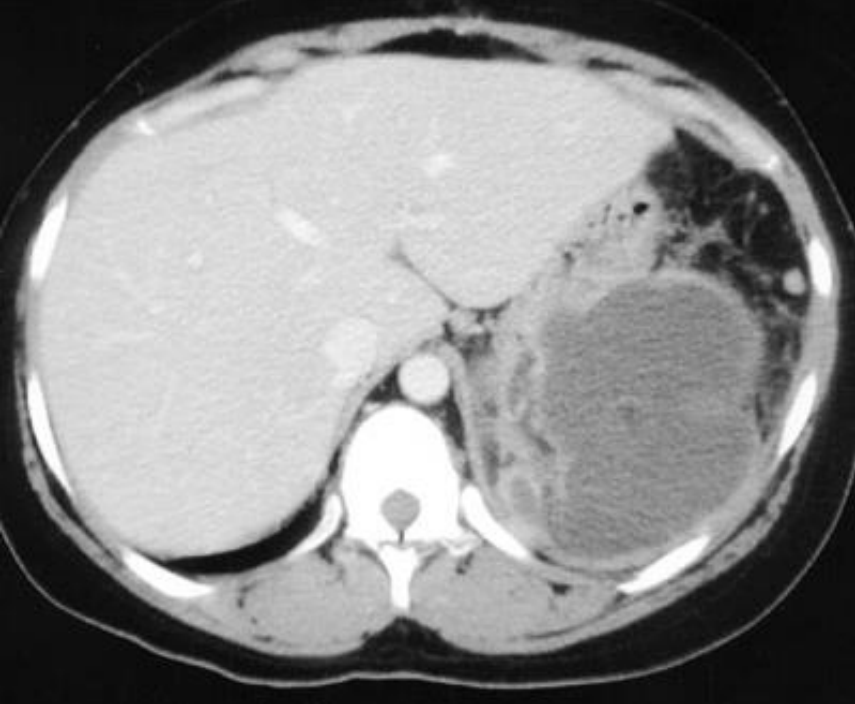
Surgical wound infections



Patient who has suffered bowel perforation

- Development of intra-abdominal abscess is a common cause of fever
- Frequently multibacterial:
 - Gram-positive cocci
 - Gram-negative rods
 - Anaerobes, especially *Bacteroides fragilis*
- Abdominal ultrasound, and particularly computerized tomography (CT) scan should be ordered to exclude this possibility

Abdominal abscesses



Chronically ill patient

- **Decubiti ulcers** need to be considered as a source of infection
- Full examination of the **back** and **buttocks** regions should be performed for tissue breakdown and purulent discharge
- Organisms associated with deep decubiti ulcers include those responsible of late postoperative infection and anaerobes, including *Bacteroides fragilis*

Decubiti ulcers



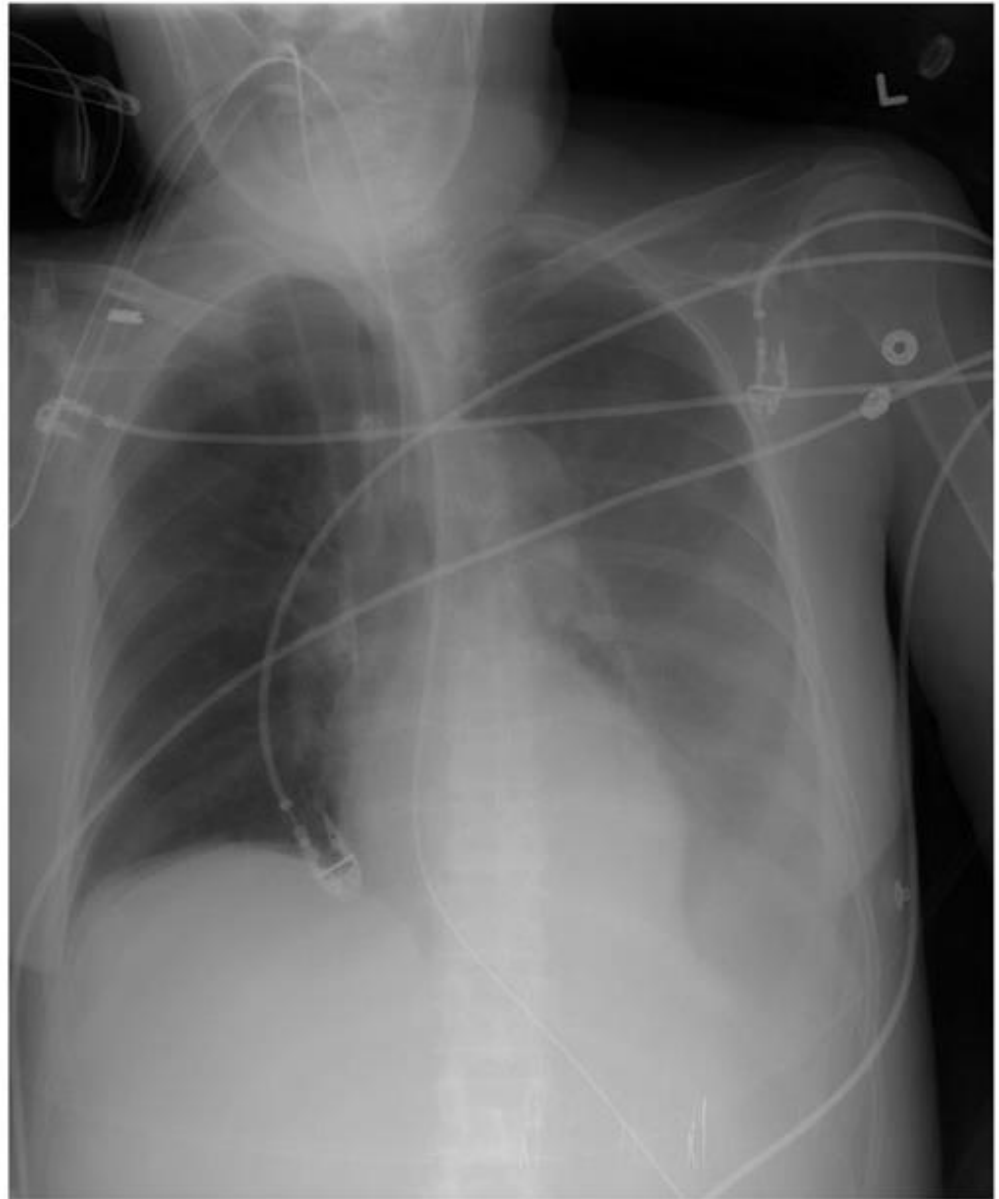
Respiratory infections in intensive care patients and other debilitated patients - Pathogenesis

- Bacteria colonizing the nasopharynx can readily gain entry to the bronchi and pulmonary parenchyma, causing bronchitis and pneumonia
- Factors favoring
 - Tracheal intubation
 - Sedatives
 - Stroke and other diseases
- Differential of infection and colonization difficult

Respiratory infections in intensive care patients and other debilitated patients - Diagnosis

- Sputum tests:
 - Presence of at least one organism on gram stain, combined with **more than 10 neutrophils per high-power field**, strongly suggests infection
 - Culture identifies the offending organism and sensitivities to antibiotics
- Chest X-ray, a new infiltrate suggests pneumonia
- Arterial blood gases, reduction in arterial Pa O₂, suggests pneumonia

Ventilator
associated
pneumonia



Line related fever – Prevalence and management

- Most hospitalized patients have one or more of these venous (and arterial) catheters or lines in place
- They are always at risk of becoming infected, and they are a common cause of fever in hospitalized patients
- At onset of fever, all venous (and arterial) lines should be examined for erythema, warmth, and exudate
- Particularly in the patient who has developed shock, all lines should be **removed** and appropriate empiric antibiotic coverage instituted immediately



Line infection

Line related fever - Causes

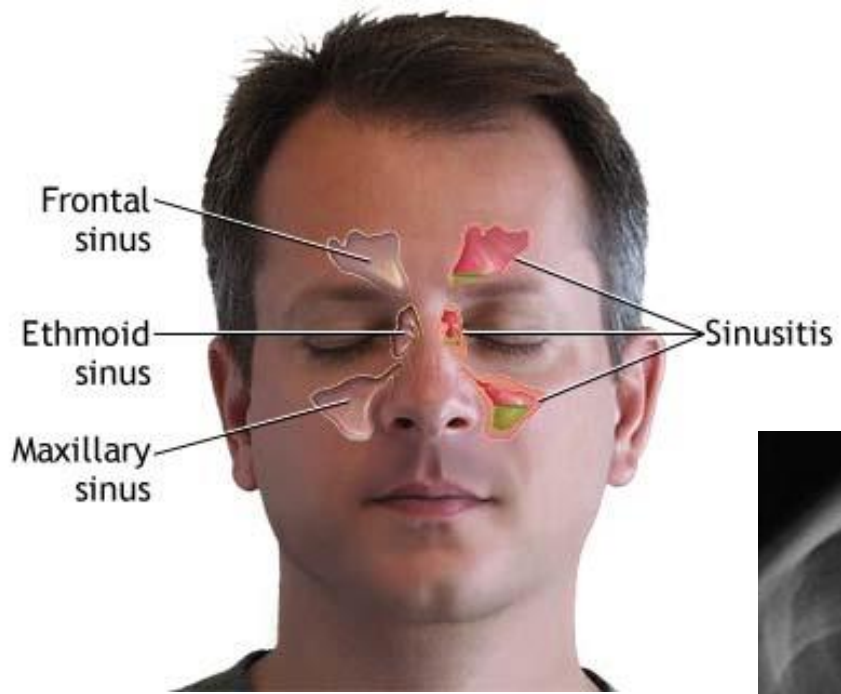
- ***Staphylococcus aureus*, *Staphylococcus epidermidis*, and gram-negative rods**
- *Candida* spp., in patients who
 - have been in the hospital for prolonged periods
 - have received multiple antibiotics

Bladder catheter related fever

- A major infectious cause of fever in hospitalized patients
- **Nearly all** patients with bladder catheters develop urinary tract infections within 30 days, despite the use of closed urinary collecting systems
- **Urinalysis** and **urine culture** need to be part of the fever workup in all patients with urinary catheters

Sinusitis

- Nasogastric and other tubes placed through the nasal passage, may occlude the ostia draining the air sinuses which can lead to sinusitis and fever
- Fever workup in these patients must include sinus films
- If sinusitis is discovered:
 - The tube must be removed from the nasal passage
 - Appropriate antibiotic coverage must be instituted



Maxillary sinusitis

Normal



Noninfectious causes of fever

- Pulmonary emboli
- Drugs, almost any of them, including antibiotics, may cause it
- Undrained collections of blood
- Inflammatory diseases
- Other

Antibiotic therapy

- Empiric antibiotic coverage must be individualized to take into account:
 - The patient **history, physical exam, test results**, etc.
 - The prevailing bacterial flora in each hospital unit
 - The history of antibiotic use in the patient
- Generally guided by **gram stain**, if gram unavailable, antibiotics should be active against gram-positive and gram-negative bacteria
- Empiric antibiotic coverage needs to be **streamlined** once culture data are available

Antibiotic related problems

- **Selection of highly resistant bacterial pathogens**
- Candidemia
- *Clostridium difficile* colitis
- Side effects

Hospitalized patient requires a systematic diagnostic approach and the judicious use of antibiotics. **Too often, patients are covered unnecessarily for prolonged periods, using broad-spectrum antibiotics**

Fever of undetermined origin

Approach of the problem

- Remains one of the great challenges in infectious diseases
- Requires a thoughtful diagnostic approach by a highly experienced clinician
- Requires a team approach in which all caregivers repeatedly share their daily findings and continually generate and test new hypotheses

Definition

- The name “fever of undetermined origin” (FUO) carries with it specific criteria and should not be loosely applied
- As first defined in 1961, FUO requires that the patient have all the following:
 - An illness that has lasted at least 3 weeks
 - Fever of more than 38.3°C (101 °F) on several occasions
 - No diagnosis after routine workup for 3 days in hospital **or after 3 or more outpatient visits**

Before diagnosing FUO ...

- Carefully document that the patient fulfills the criteria
- The patient should be instructed to measure both 6-AM and 6-PM temperature to rule out an exaggerated circadian rhythm
- An electronic thermometer should always be used to exclude the possibility of factitious fever

Pattern of fever

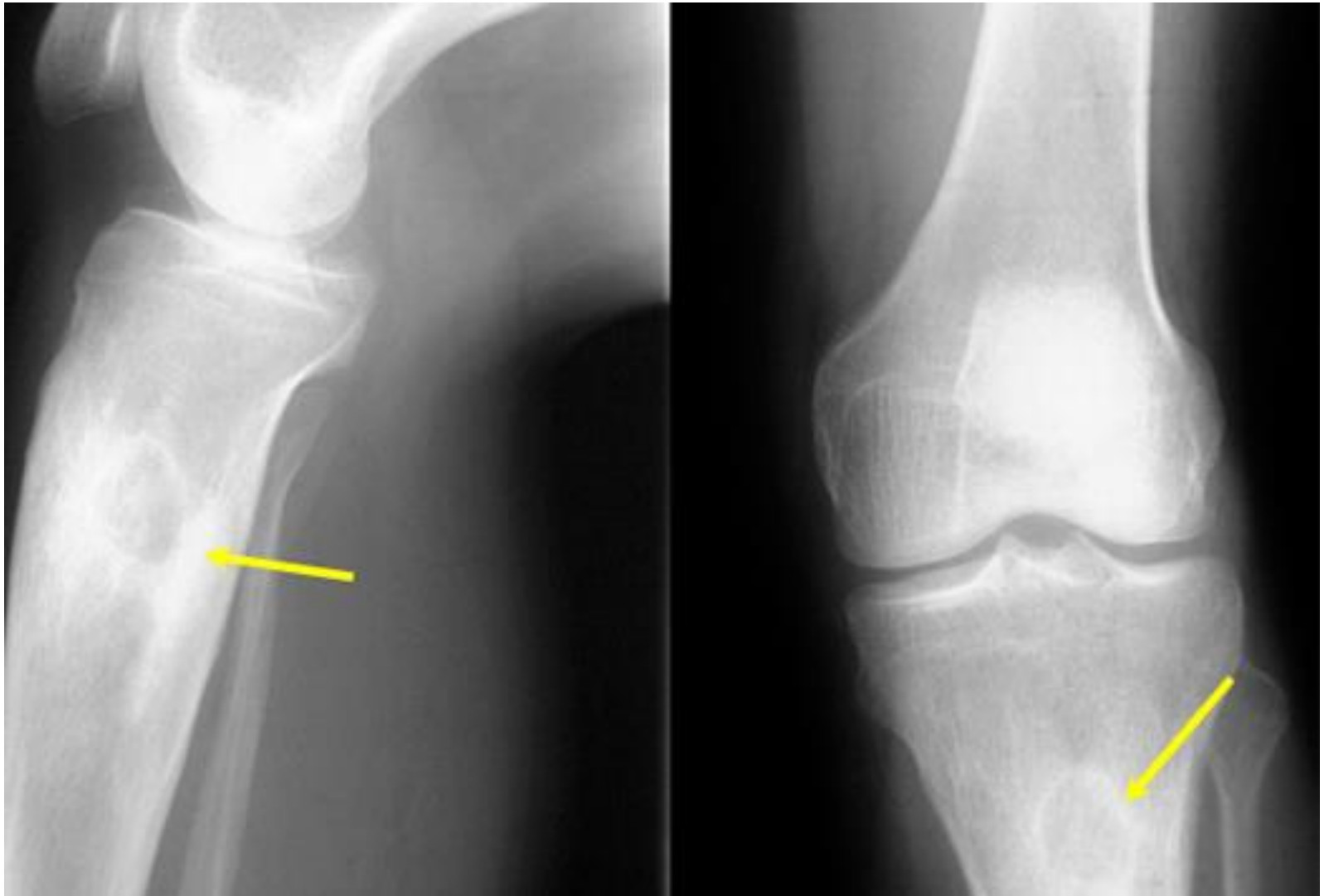
- Generally **not helpful** in identifying the fever's cause
- Patients with daily fever are more likely to be diagnosed as compared to those with intermittent or periodic fever
- Fever repeatedly highest in the early morning suggests:
 - Miliary tuberculosis
 - Typhoid fever
 - Periarteritis nodosa

Groups of causes of FUO

- Infections
- Neoplasms
- Autoimmune disorders
- Miscellaneous

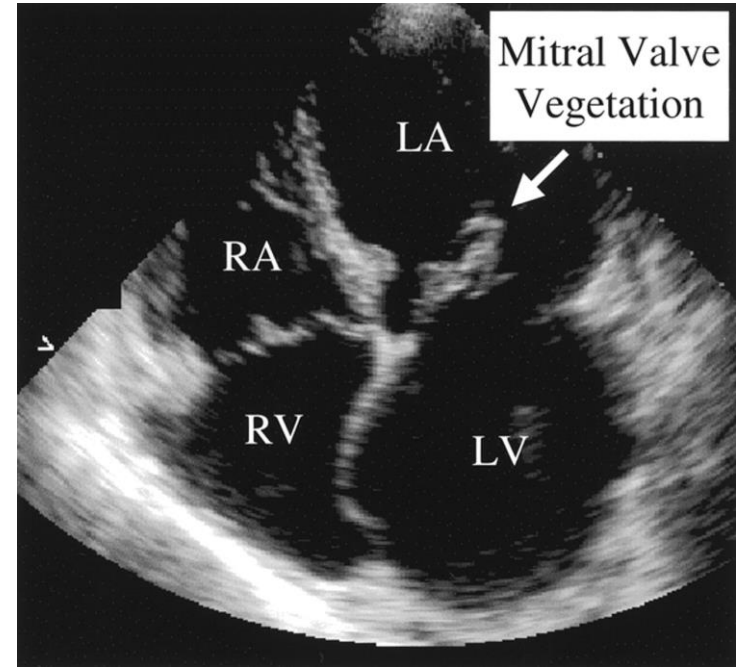
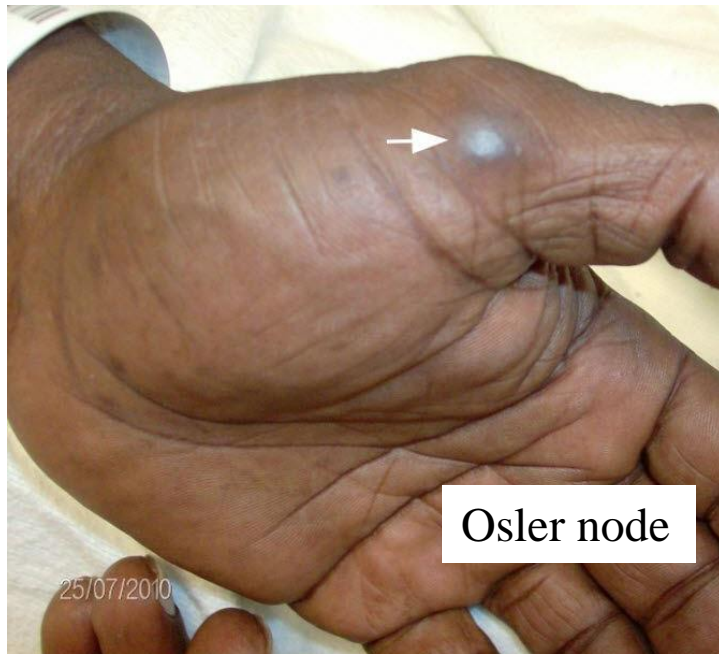
Infections causing FUO - I

- **Abscesses**, particularly abdominal abscesses that may persist for prolonged periods before being diagnosed
- **Osteomyelitis**, particularly of the vertebral bodies, mandible, and air sinuses
- **Subacute bacterial endocarditis**, less common now with improved Micro and Echo tests
- **Biliary system infections**, sometime with no right upper quadrant pain or tenderness
- **Subacute pyelonephritis**, can present with absence of dysuria, frequency, or flank pain



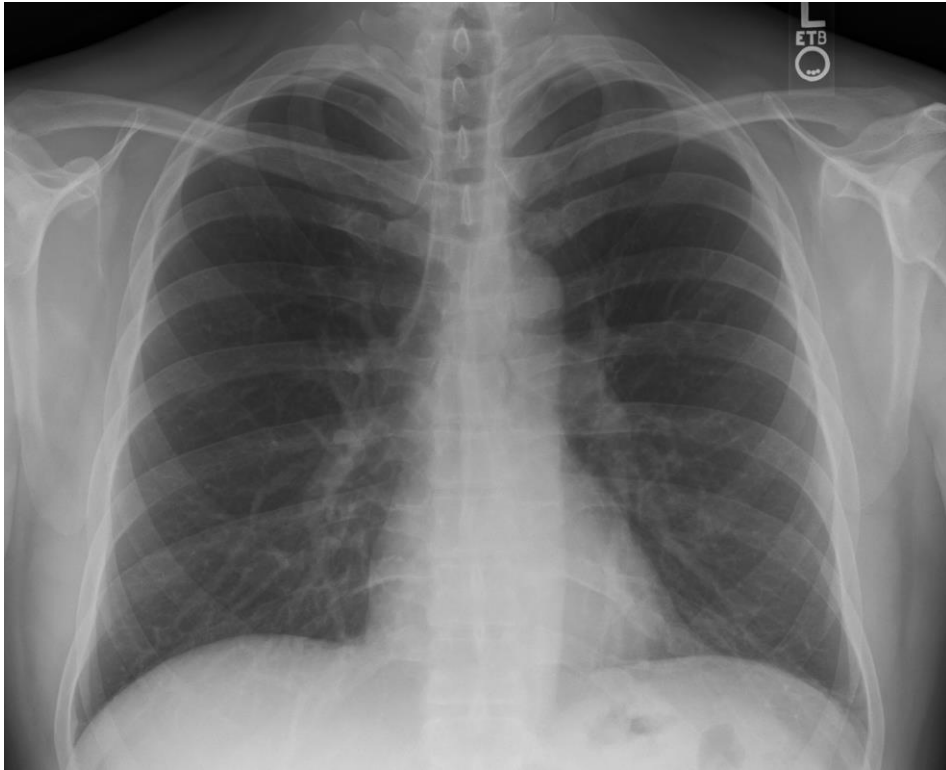
Osteomyelitis

Subacute bacterial endocarditis

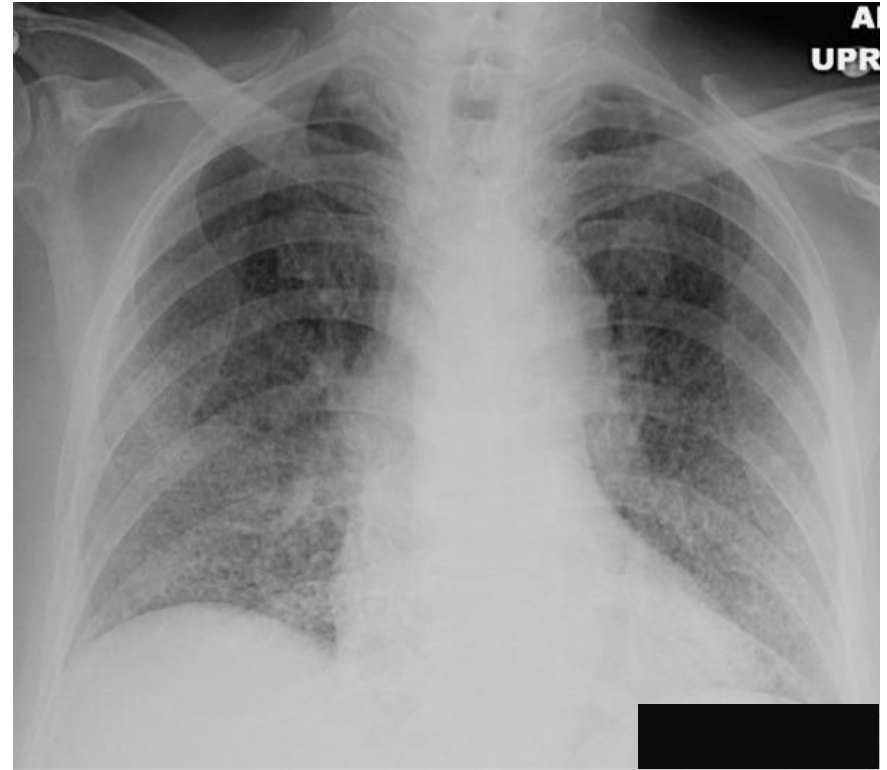


Infections causing FUO - II

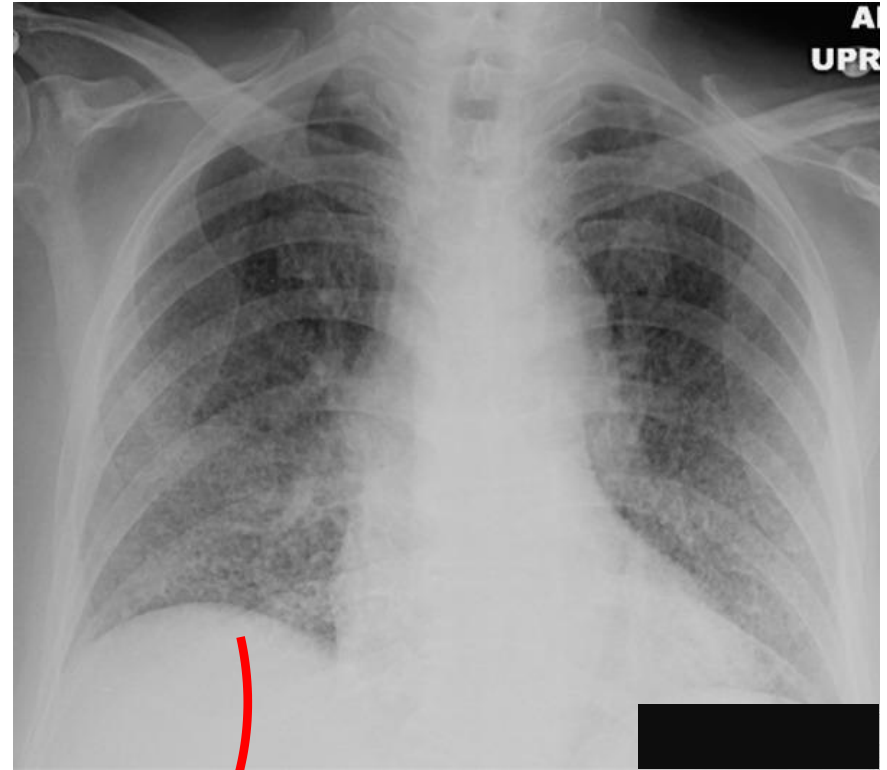
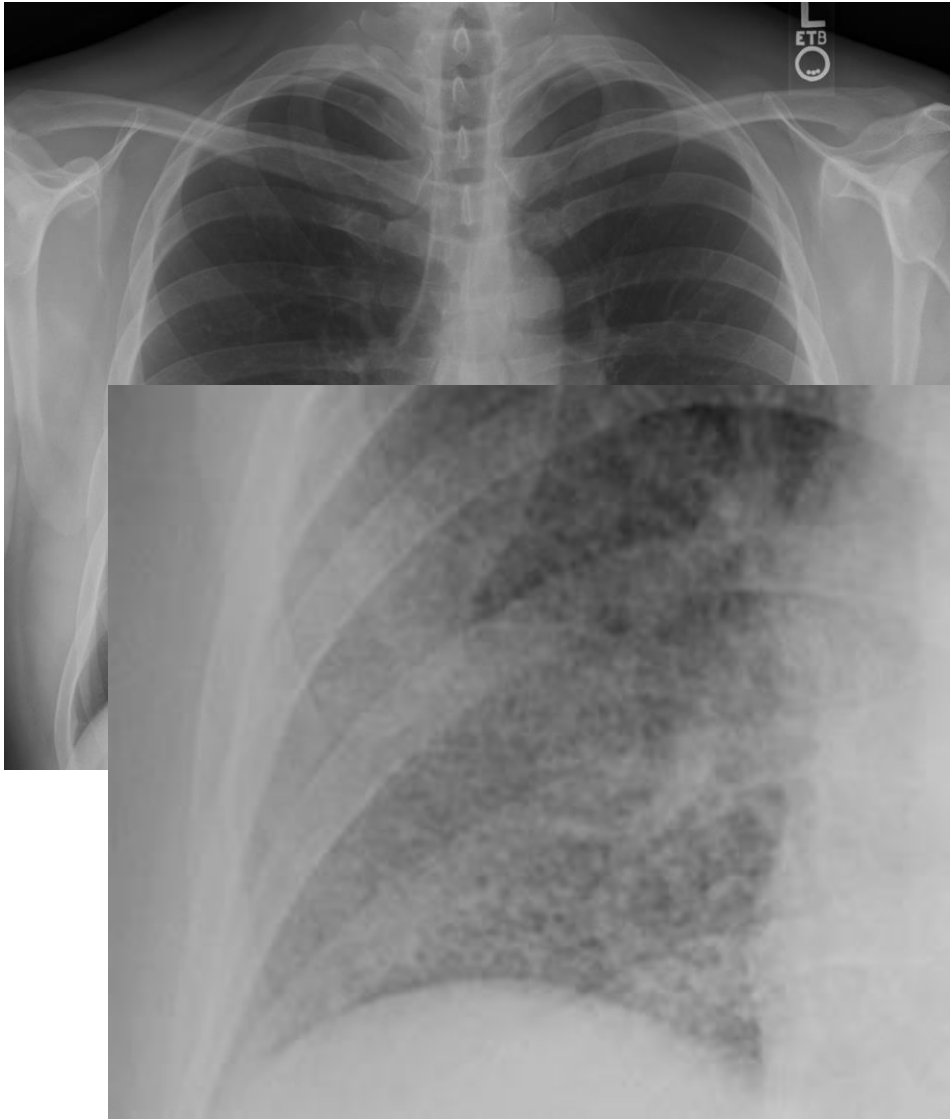
- **Miliary tuberculosis**, in elderly and immunocompromised, such as patients with HIV, on high-dose glucocorticoids or a tumor necrosis factor (TNF) inhibitor
- Spirochetal diseases, such as **leptospirosis**, **Lyme disease** and **relapsing fever**
- **Brucellosis**, by eating unpasteurized cheese
- **Rickettsial** infections, history of tick bite
- ***Chlamydia psittaci***, contracted from birds



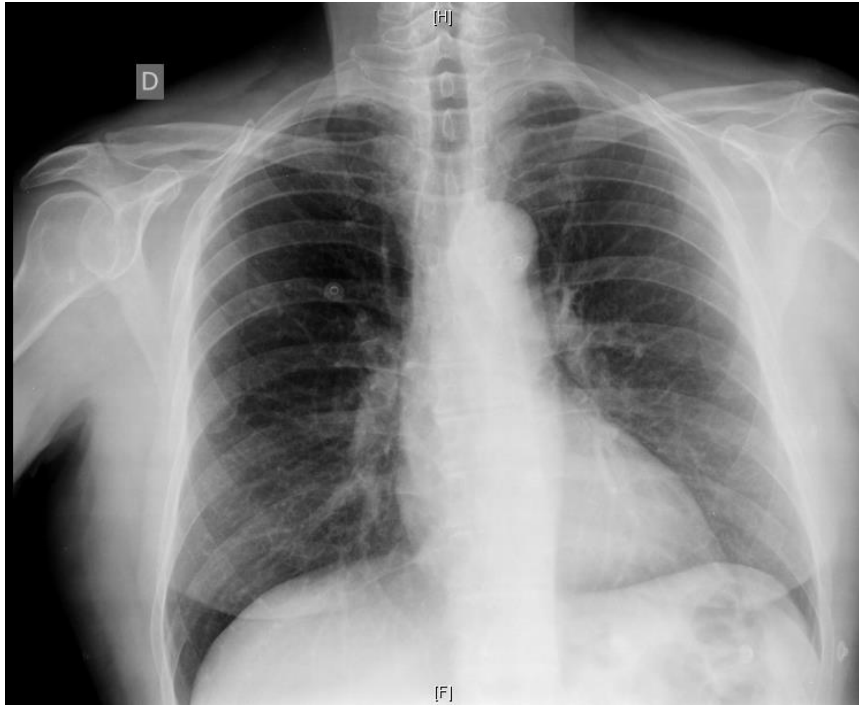
Normal



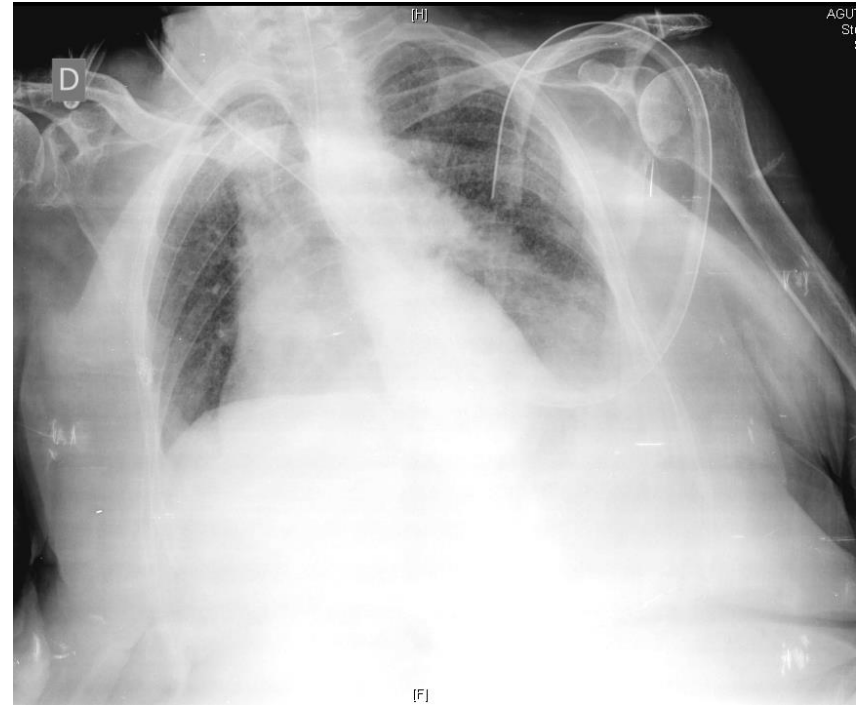
Miliary tuberculosis



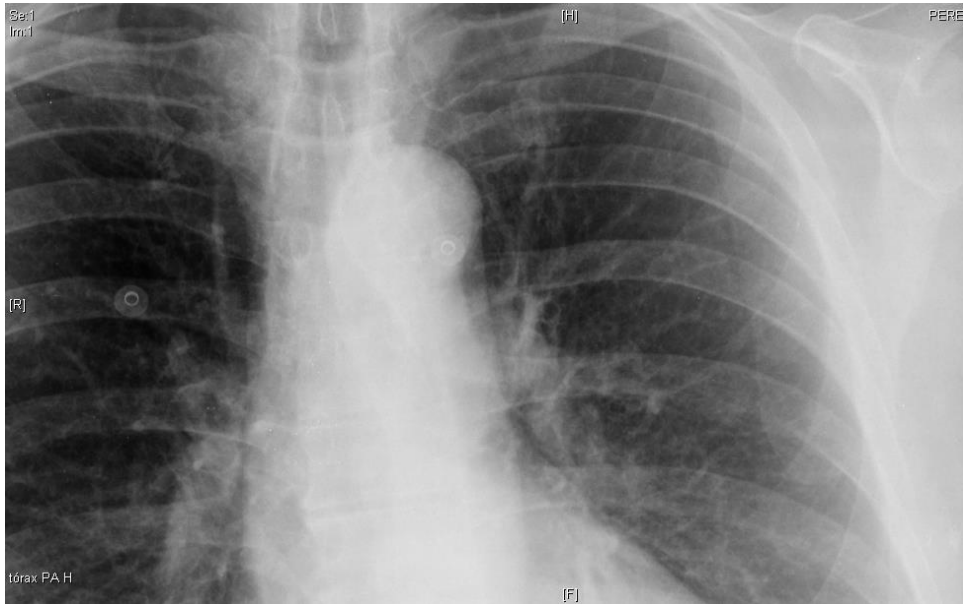
Miliary tuberculosis



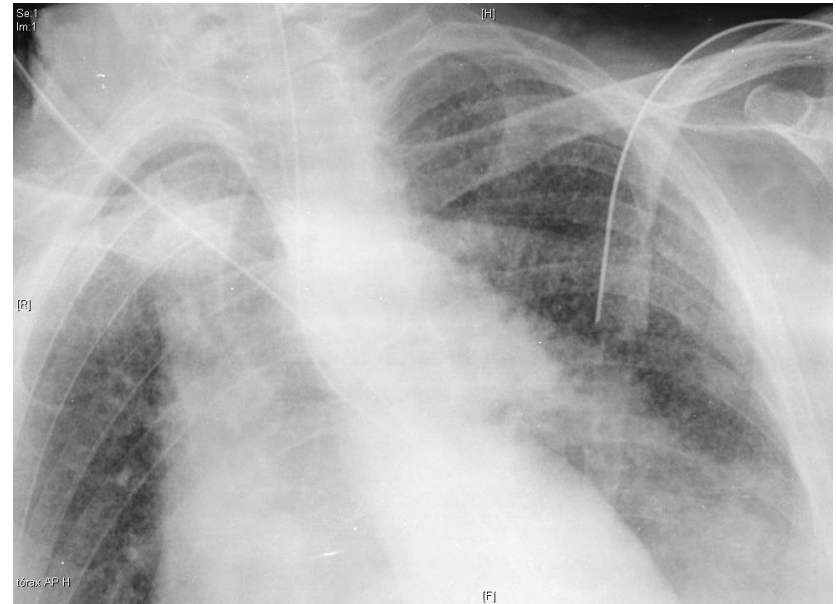
Normal



Miliary tuberculosis



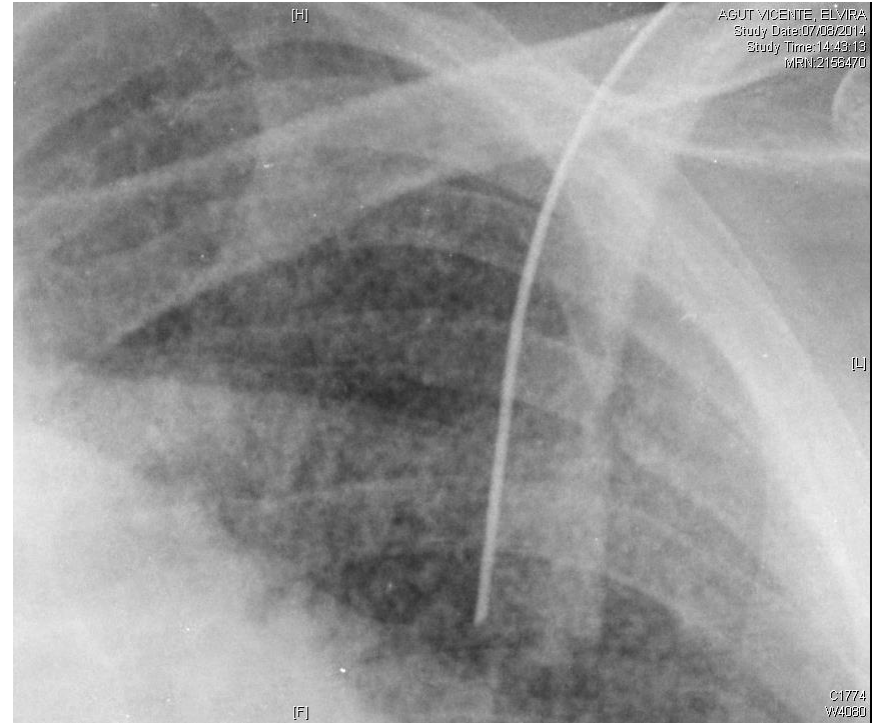
Normal



Miliary tuberculosis



Normal



Miliary tuberculosis

Infections causing FUO - III

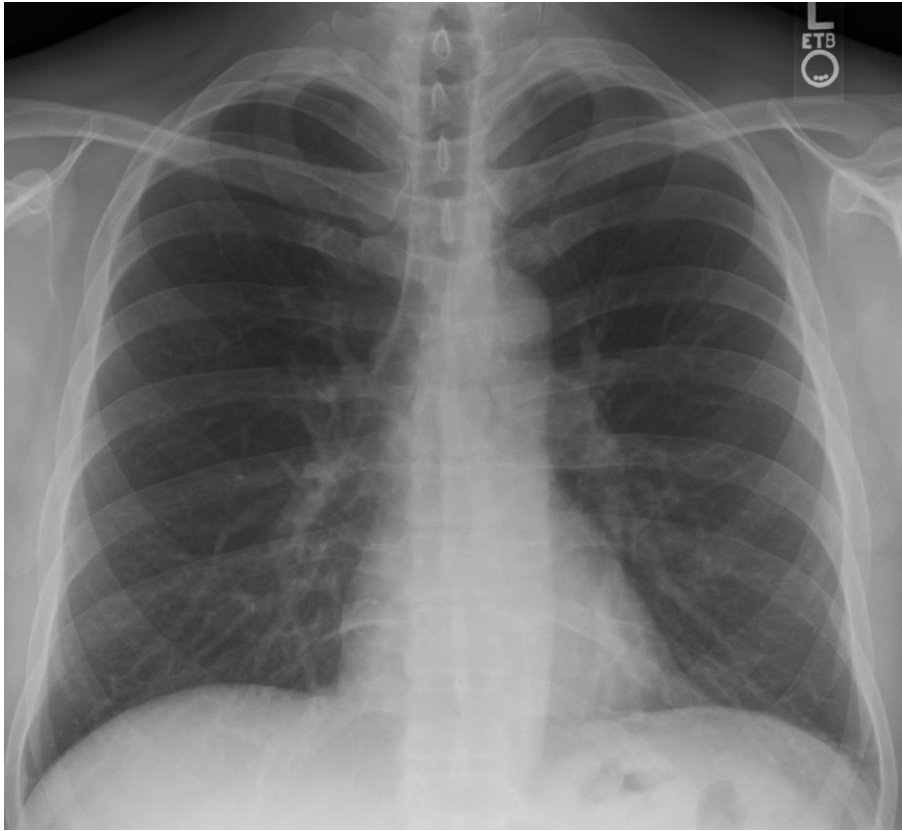
- **Epstein–Barr virus** and **cytomegalovirus** can both cause a mononucleosis síndrome
- **Cryptococcosis** and **histoplasmosis** being the two most common fungal diseases reported
- Parasites, such as **malaria** (nonfalciparum forms), **leishmaniasis**, **toxoplasmosis**, and **trypanosomiasis**

Infections and FUO

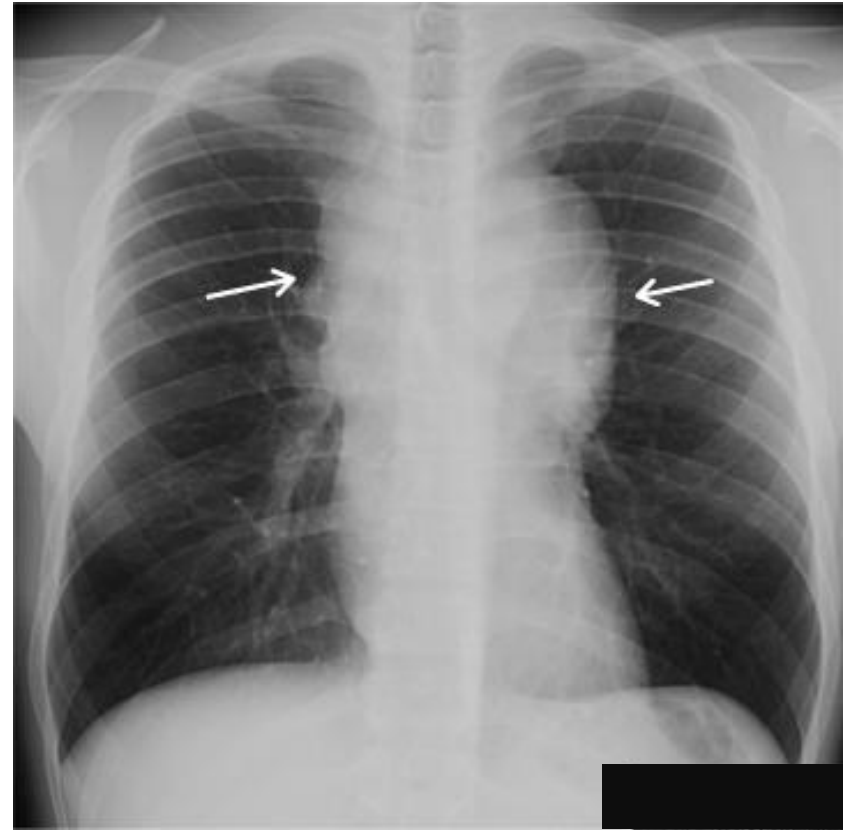
- Infection is the most common cause of FUO in patients **under 65** years of age
- Helpful **epidemiology** circumstances: animal exposure, insect bites, outdoor camping, travel, and exposure to infected humans
- Useful clues that may provide **physical exam**: cardiac auscultation, and inspection of skin, nail beds, and fundi
- Prior **antibiotic** administration **interferes** with diagnosis

Neoplasms causing FUO

- **Hodgkin's lymphoma**, intermittently produce pyrogens: the patient may be afebrile, and then may have hectic fevers, known as Pel-Ebstein fever
- Non-Hodgkin lymphoma
- Leukemia
- Renal cell carcinoma (formerly hypernephroma)
- Hepatocarcinoma
- Atrial myxoma
- Neoplasms are the most common cause of FUO in patients **over 65** years of age

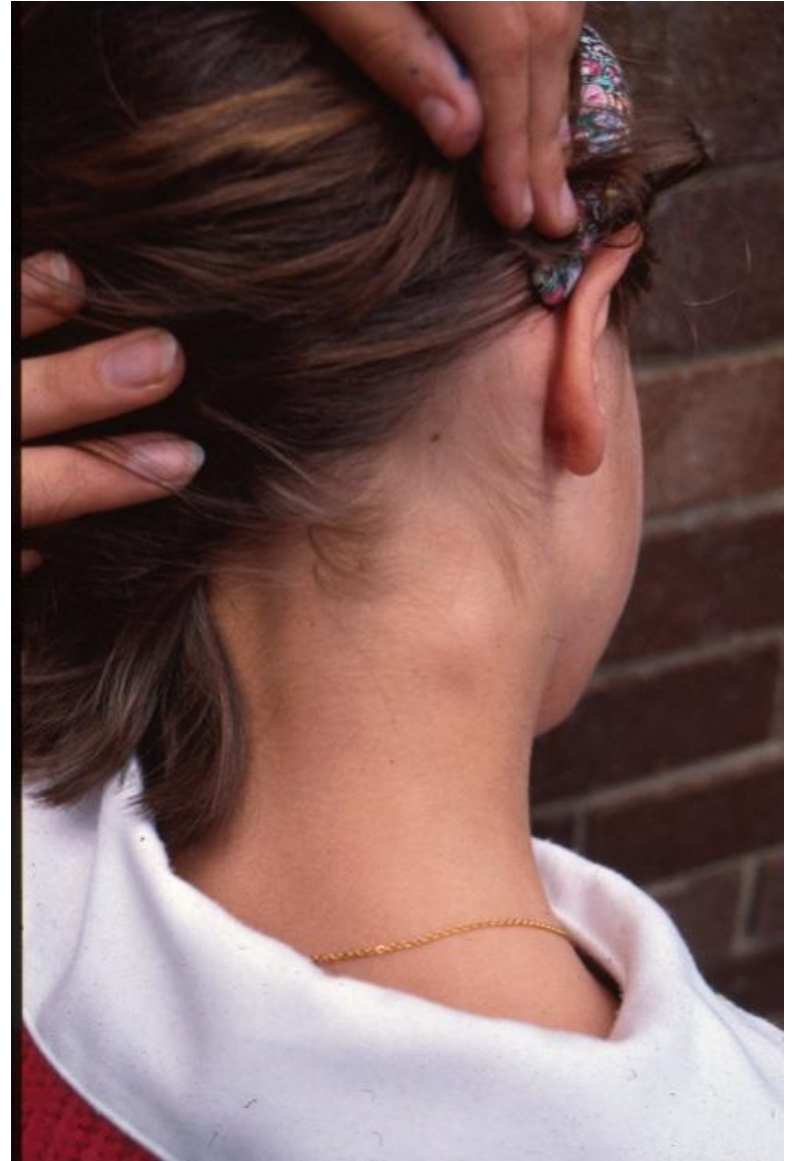


Normal



Hodgkin's lymphoma

Cervical lymphadenopathies



Autoimmune Disease causing FUO

- **Still's disease:** evanescent macular rash, arthralgias, sore throat, leukocytosis, etc. ; no specific diagnostic test
- Systemic lupus erythematosus
- Polymyalgia rheumatica and temporal arteritis, old patients
- Polyarteritis nodosa, hypersensitivity angiitis and other vasculitis
- Mixed connective tissue disease
- Subacute thyroiditis
- Kikuchi's disease, or histiocytic necrotizing lymphadenitis

Still's disease,
evanescent
macular rash



Miscellaneous causes of FUO

- **Drug fever**
 - **Phenytoin**
 - Quinidine sulfate and procainamide
 - Sulfonamides and beta-lactams
- Familial mediterranean fever, lack of **pyrin** or marenosttrin, a cytokine inhibitor
- Pulmonary emboli
- Factitious fever
- No cause found in some cases, but generally fever spontaneously subsides

Diagnostic Workup of FUO

General approach

- Laboratory tests, imaging studies and other tests should be **guided by history and physical exam**
- Because each case is different, a series of yes-or-no branch points or diagrams are not useful for guiding diagnosis
- An **iterative** approach to testing and analysis is most effective
- The clinician must review each new potential diagnostic clue and assess its significance in relationship to the patient's other positive findings

History

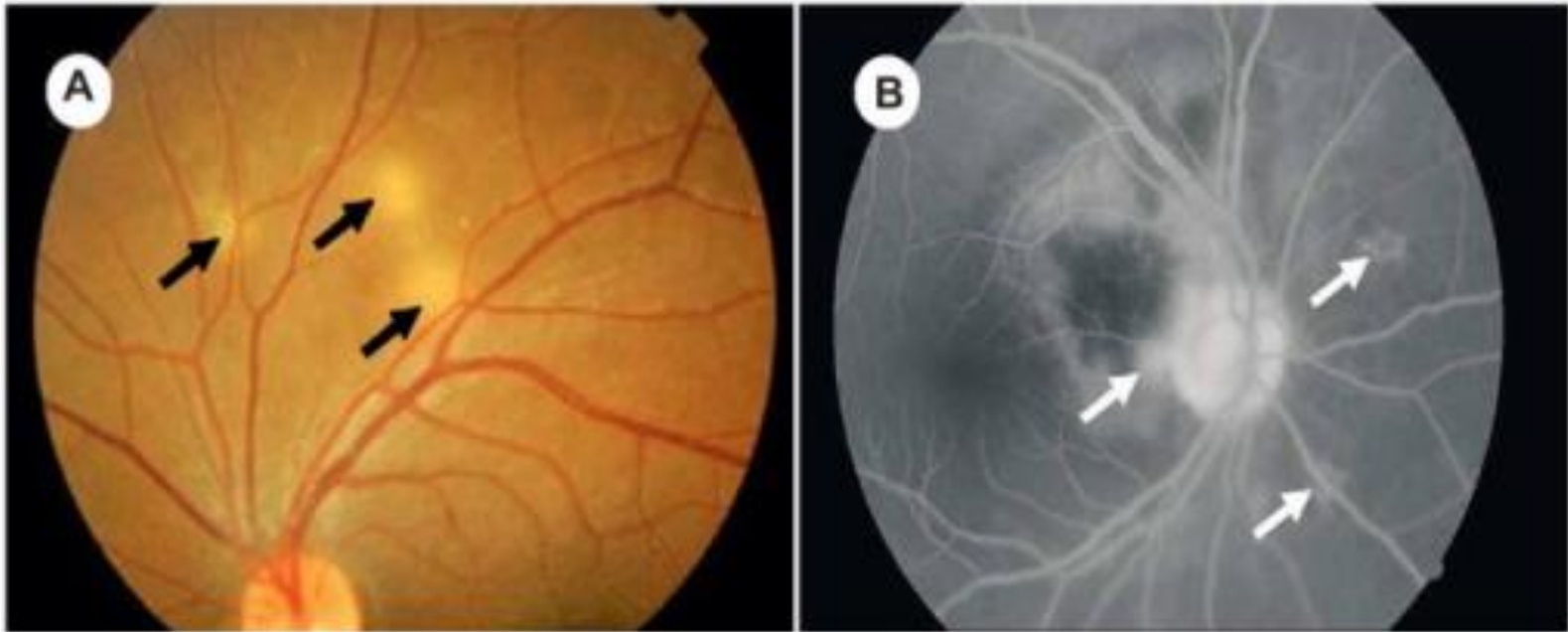
- Present and past history
 - Play a critical role in narrowing the differential diagnosis and deciding on the most appropriate diagnostic tests
 - A review of symptoms needs to be periodically updated
- Family history
- Medications and other substances taken
- Social history
 - Pets, insect bites
 - Travel, hobbies

Physical examination

- Careful physical examination is frequently helpful
- Must be repeated regularly
- Particular attention should be paid to:
 - Skin: embolic or vasculitic lesions
 - Nail beds: small emboli
 - Joints: motion and effusions
 - Eyes: conjunctival petechiae, uveitis, choroidal tubercles, etc.
 - Lymph nodes



Splinter hemorrhages



Choroidal tubercles: A) ophthalmoscopic pictures, black arrows; B) fluorescein angiogram, white arrows.

Common laboratory tests

- Complete blood count with differential
- C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
- Liver function tests, lactic dehydrogenase (LDH), creatine phosphokinase (CPK)
- Antinuclear antibodies and rheumatoid factor
- Serum protein electrophoresis
- Urinalysis and urine culture
- Blood cultures ×3, held for three weeks

Imaging studies

- **Chest** and other radiographs
- **Abdominal**, cardiac and other ultrasound
- Computed tomography (CT) scan of chest and abdomen
- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET) / CT scan with ^{18}F fluorodeoxyglucose
- Radionuclide scans: Ga, In tagged white blood cells

Other studies - I

- Tuberculin skin test or interferon γ release assay
- Sputum: gram, acid fast, and culture
- Biopsy and culture * of bone marrow, lymph nodes or other tissues
- Viral cultures or quantitative polymerase chain reaction (PCR) may also be considered in specific cases, such as cytomegalovirus or Epstein-Barr virus suspected infections

* Aerobic, anaerobic, mycobacterial, and fungal

Other studies - II

- Peripheral blood smears with Giemsa and Wright stains
- Stool smears for ova and parasites
- **HIV antibody**, and HIV viral load
- Serologies, generally two samples
- Laparoscopic guided biopsy
- Temporal artery biopsy
- At times the wisest course of action is **to wait**

Treatment of FUO

- Antipyretics can be administered, in most cases on a regular schedule
- **Antibiotics** are generally **contraindicated** until a specific diagnosis is made
- **Glucocorticoids** best **avoided** until a specific diagnosis is made

Prognosis of FUO

- Delay in diagnosis may worsen the outcome in
 - Intra-abdominal abscess
 - Miliary tuberculosis
 - Pulmonary emboli
- If these diseases are carefully excluded, lack of a diagnosis after an extensive workup is associated with a 5-year mortality of only 3%
- Prognosis is somewhat **worse** in **elderly** patients because of their increased risk of malignancy

FUO in the HIV-infected patient

- Primary HIV infection can present with prolonged fever, diagnosis: HIV viral load
- In the later stages prolonged fever is common:
 - Bacterial and **mycobacterial** infections
 - Cytomegalovirus
 - *Pneumocystis jiroveci*
 - Toxoplasmosis and cryptococcosis
 - Leishmaniasis
 - Lymphoma
 - Drug fever

Key messages

To remember...

- Fever is a very common clinical presentation in most clinical settings
- Causes of fever are myriad, but a clinical history and a physical exam allow a quick diagnosis in most cases and guides about further testing in all other cases

Further reading

Used references

- **Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 3.**
- Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill, 2012. Chapters 16 and 18.

Preparing the exam

- Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 3.
- These slides