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FEVER of Unknown Origin

OVERVIEW

- Definition
- Etiology & Epidemiology
- Differential Diagnosis
- Approach to a patient
  - Algorithm
  - First stage diagnostic tests
  - FDG PET/CT
  - Later stage diagnostic tests
- Treatment
- Prognosis

Definition:

FUO is now defined as:

1. Fever ≥38.3°C (>101°F) on at least two occasions.
2. Illness duration of ≥3 weeks.
3. No known immunocompromised state.
4. Diagnosis remain uncertain after a thorough history taking, physical examination, and following obligatory investigations:

1. ESR
2. CRP
3. CBC
4. Electrolytes
5. Creatinine
6. Total Protein
7. ALP
8. AST
9. ALT
10. LDH
11. Creatine Kinase
12. Ferritin
13. ANA and RF
14. Protein electrophoresis
15. Urinalysis
16. Blood culture (3 samples)
17. Urine culture
18. Chest X-ray
19. USG Abdomen
20. Tuberculin Skin Test (TST) or Interferon γ release assay (IGRA)

Inflammation of unknown origin

- Presence of **elevated inflammatory parameter(CRP or CRP)** on multiple occasion for a period of **at least 3 weeks** in an immunocompetent patient with normal body temperature, for which final explanation is lacking despite **history-taking, physical examination, and the obligatory tests**

Causes:

1. Infections.
2. Non – Infectious Inflammatory Disease (NIIDs).
3. Neoplasms.
4. Miscellaneous causes.

ETIOLOGY AND EPIDEMIOLOGY

- Most common cause in Non western countries : Infection and among them most common cause is mycobacterium TB
- Most common cause in western countries: Noninfectious inflammatory diseases and these are
  - Autoimmune
  - Auto inflammatory
  - Granulomatous
  - Vasculitis

Causes continue

- Infections (40% cases)
- Neoplasm (20% cases)
- NIIDs (20%)
- Miscellaneous Causes(10%)
- Undiagnosed(10%)

On study show a western Cohort that in PUO 1/3 of cases remains undiagnosed and 2/3 of cases usually get diagnosed due availability of Advance testing and scans

INFECTIONS:

Bacterial: Tuberculosis, atypical mycobacterium infection, Leptospirosis, Typhoid, Syphilis, Infective endocarditis, Q fever, etc.

Viral: HIV, Hepatitis, Herpes, Dengue, etc.

Parasitic: Malaria, Toxoplasmosis, Amoebiasis, Schistosomiasis, etc.

Fungal: Aspergillosis, Candidiasis, Mucormycosis, Cryptococcus, etc.

Infections:

Infections	
Bacterial, nonspecific	Abdominal abscess, adnexitis, apical granuloma, appendicitis, cholangitis, cholecystitis, diverticulitis, endocarditis, endometritis, epidural abscess, infected joint prosthesis, infected vascular catheter, infected vascular prosthesis, infectious arthritis, infective myonecrosis, intracranial abscess, liver abscess, lung abscess, malakoplakia, mastoiditis, mediastinitis, mycotic aneurysm, osteomyelitis, pelvic inflammatory disease, prostatitis, pyelonephritis, pylephlebitis, renal abscess, septic phlebitis, sinusitis, spondylodiscitis, xanthogranulomatous urinary tract infection
Bacterial, specific	Actinomycosis, atypical mycobacterial infection, bartonellosis, brucellosis, *Campylobacter* infection, *Chlamydia pneumoniae* infection, chronic meningococcemia, ehrlichiosis, gonococcemia, legionellosis, leptospirosis, listeriosis, louse-borne relapsing fever (*Borrelia recurrentis*), Lyme disease, melioidosis (*Pseudomonas pseudomallei*), *Mycoplasma* infection, nocardiosis, psittacosis, Q fever (*Coxiella burnetii*), rickettsiosis, *Spirillum minor* infection, *Streptobacillus moniliformis* infection, syphilis, tick-borne relapsing fever (*Borrelia duttonii*), tuberculosis, tularemia, typhoid fever and other salmonelloses, Whipple's disease (*Tropheryma whipplei*), yersiniosis
Fungal	Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, *Malassezia furfur* infection, paracoccidioidomycosis, *Pneumocystis jirovecii* pneumonia, sporotrichosis, zygomycosis
Parasitic	Amebiasis, babesiosis, echinococcosis, fascioliasis, malaria, schistosomiasis, strongyloidiasis, toxocariasis, toxoplasmosis, trichinellosis, trypanosomiasis, visceral leishmaniasis
Viral	Colorado tick fever, coxsackievirus infection, cytomegalovirus infection, dengue, Epstein-Barr virus infection, hantavirus infection, hepatitis (A, B, C, D, E), herpes simplex, HIV infection, human herpesvirus 6 infection, parvovirus infection, West Nile virus infection

Non – Infectious Inflammatory Disease (NIIDs):

Noninfectious Inflammatory Diseases	
Systemic rheumatic and autoimmune diseases	Ankylosing spondylitis, antiphospholipid syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behçet's disease, cryoglobulinemia, dermatomyositis, Felty syndrome, gout, mixed connective-tissue disease, polymyositis, pseudogout, reactive arthritis, relapsing polychondritis, rheumatic fever, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome
Vasculitis	Allergic vasculitis, eosinophilic granulomatosis with polyangiitis, giant cell vasculitis/polymyalgia rheumatica, granulomatosis with polyangiitis, hypersensitivity vasculitis, Kawasaki disease, polyarteritis nodosa, Takayasu arteritis, urticarial vasculitis
Granulomatous diseases	Idiopathic granulomatous hepatitis, sarcoidosis
Autoinflammatory syndromes	Adult-onset Still's disease, Blau syndrome, CAPS[b] (cryopyrin-associated periodic syndromes), Crohn's disease, DIRA (deficiency of the interleukin 1 receptor antagonist), familial Mediterranean fever, hemophagocytic syndrome, hyper-IgD syndrome (HIDS, also known as mevalonate kinase deficiency), juvenile idiopathic arthritis, PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne), PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis), recurrent idiopathic pericarditis, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis), Schnitzler syndrome, TRAPS (tumor necrosis factor receptor–associated periodic syndrome)

Neoplasms

Neoplasms	
Hematologic malignancies	Amyloidosis, angioimmunoblastic lymphoma, Castleman's disease, Hodgkin's disease, hypereosinophilic syndrome, leukemia, lymphomatoid granulomatosis, malignant histiocytosis, multiple myeloma, myelodysplastic syndrome, myelofibrosis, non-Hodgkin's lymphoma, plasmacytoma, systemic mastocytosis, vaso-occlusive crisis in sickle cell disease
Solid tumors	Most solid tumors and metastases can cause fever. Those most commonly causing FUO are breast, colon, hepatocellular, lung, pancreatic, and renal cell carcinomas.
Benign tumors	Angiomyolipoma, cavernous hemangioma of the liver, craniopharyngioma, necrosis of dermoid tumor in Gardner's syndrome

Miscellaneous causes:

Miscellaneous Causes	
	ADEM (acute disseminated encephalomyelitis), adrenal insufficiency, aneurysms, anomalous thoracic duct, aortic dissection, aortic-enteral fistula, aseptic meningitis (Mollaret's syndrome), atrial myxoma, brewer's yeast ingestion, Caroli disease, cholesterol emboli, cirrhosis, complex partial status epilepticus, cyclic neutropenia, drug fever, Erdheim-Chester disease, extrinsic allergic alveolitis, Fabry's disease, factitious disease, fire-eater's lung, fraudulent fever, Gaucher disease, Hamman-Rich syndrome (acute interstitial pneumonia), Hashimoto's encephalopathy, hematoma, hypersensitivity pneumonitis, hypertriglyceridemia, hypothalamic hypopituitarism, idiopathic normal-pressure hydrocephalus, inflammatory pseudotumor, Kikuchi's disease, linear IgA dermatosis, mesenteric fibromatosis, metal fume fever, milk protein allergy, myotonic dystrophy, nonbacterial osteitis, organic dust toxic syndrome, panniculitis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes), polymer fume fever, post–cardiac injury syndrome, primary biliary cirrhosis, primary hyperparathyroidism, pulmonary embolism, pyoderma gangrenosum, retroperitoneal fibrosis, Rosai-Dorfman disease, sclerosing mesenteritis, silicone embolization, subacute thyroiditis (de Quervain's), Sweet syndrome (acute febrile neutrophilic dermatosis), thrombosis, tubulointerstitial nephritis and uveitis syndrome (TINU), ulcerative colitis

DIFFERENTIAL DIAGNOSIS

- Atypical presentation of common disease >> Rare diseases

  like atypical presentation of endocarditis , diverticulitis, and extra pulmonary TB then Q fever and Whipple disease which are rare condition
- Most common cancerous cause of FUO : Malignant Lymphoma
- Drug Induced fever
  - Allopurinol, carbamazepine, phenytoin, antimicrobial and quinidine
- Exercise Induced Hyperthermia
  - Increase temperature asso. With moderate to sever hyperthermia
- Factitious Fever (artificially induced)
- Fraudulent Fever (patient manipulates thermometer)

Approach to FUO:

1st step: Detailed history and physical examination:

- Contact with patient having disease (like tuberculosis).
- Travel, sexual, drug history.
- Occupational history.
- History of previous surgery or implant insertion or any other minor procedures.

- Detailed physical examination from top to bottom to find out Potentially Diagnostic Clues (PDCs). E.g., Lymphadenopathy which may give diagnostic clue after biopsy, Eschars for scrub typhus, malar rash for SLE, etc.

Next step: Do all Obligatory Investigations:

1. ESR
2. CRP
3. CBC
4. Electrolytes
5. Creatinine
6. Total Protein
7. ALP
8. AST
9. ALT
10. LDH
11. Creatine Kinase
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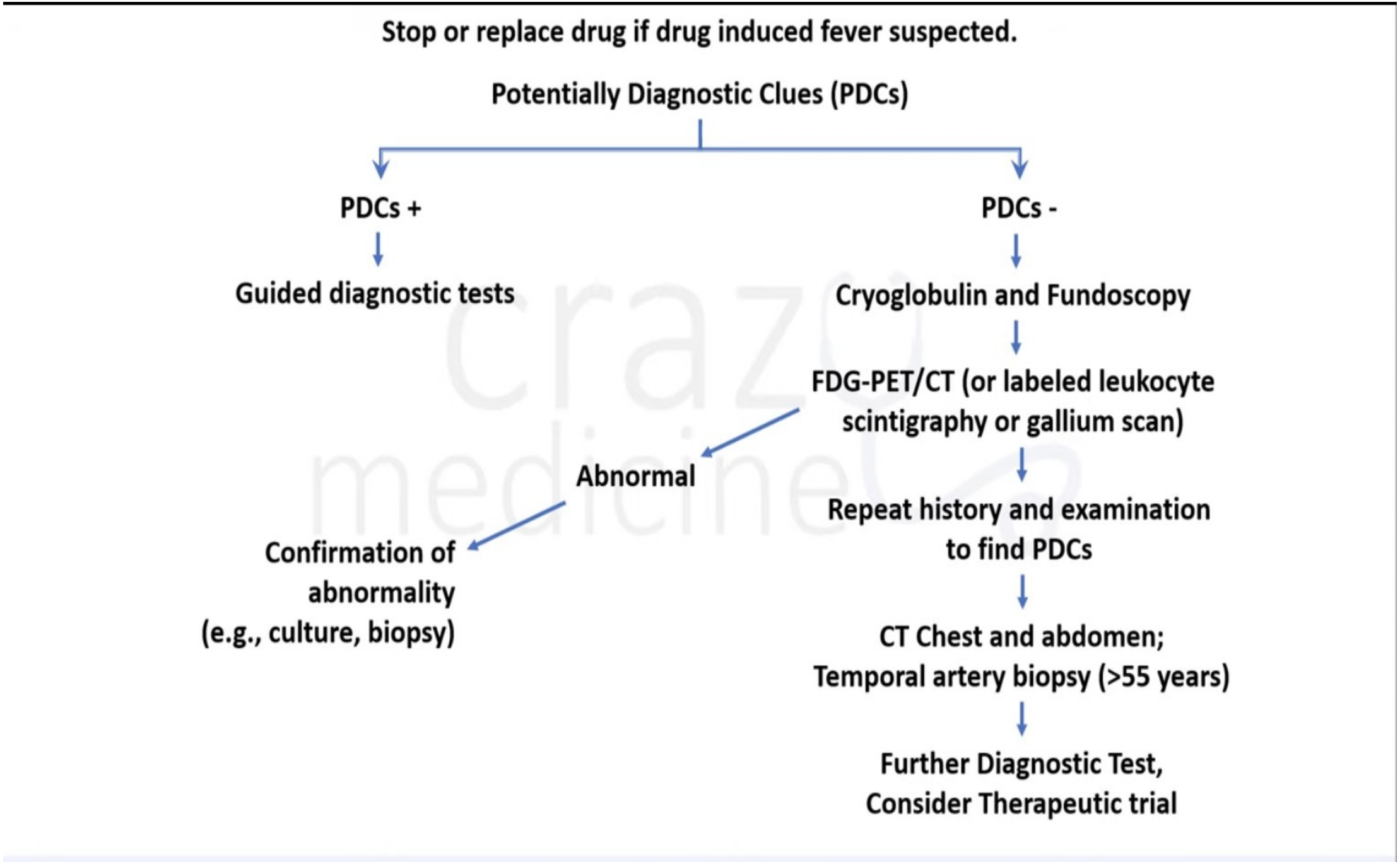
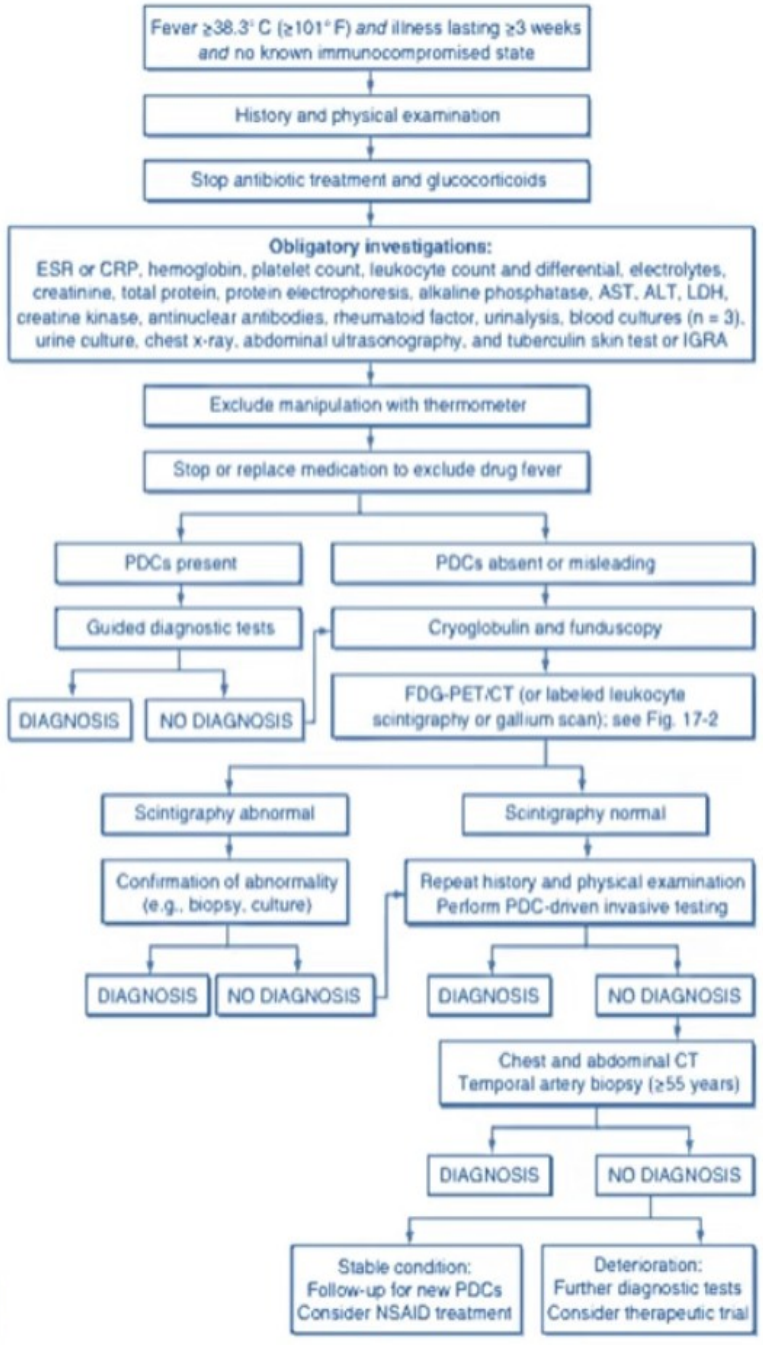

Stop or replace drug if drug induced fever suspected.
Potentially Diagnostic Clues (PDCs)
PDCs +
Guided diagnostic tests
PDCs -
Cryoglobulin and Fundoscopy
FDG-PET/CT (or labeled leukocyte scintigraphy or gallium scan)
Abnormal
Confirmation of abnormality (e.g., culture, biopsy)
Repeat history and examination to find PDCs
CT Chest and abdomen; Temporal artery biopsy (>55 years)
Further Diagnostic Test, Consider Therapeutic trial

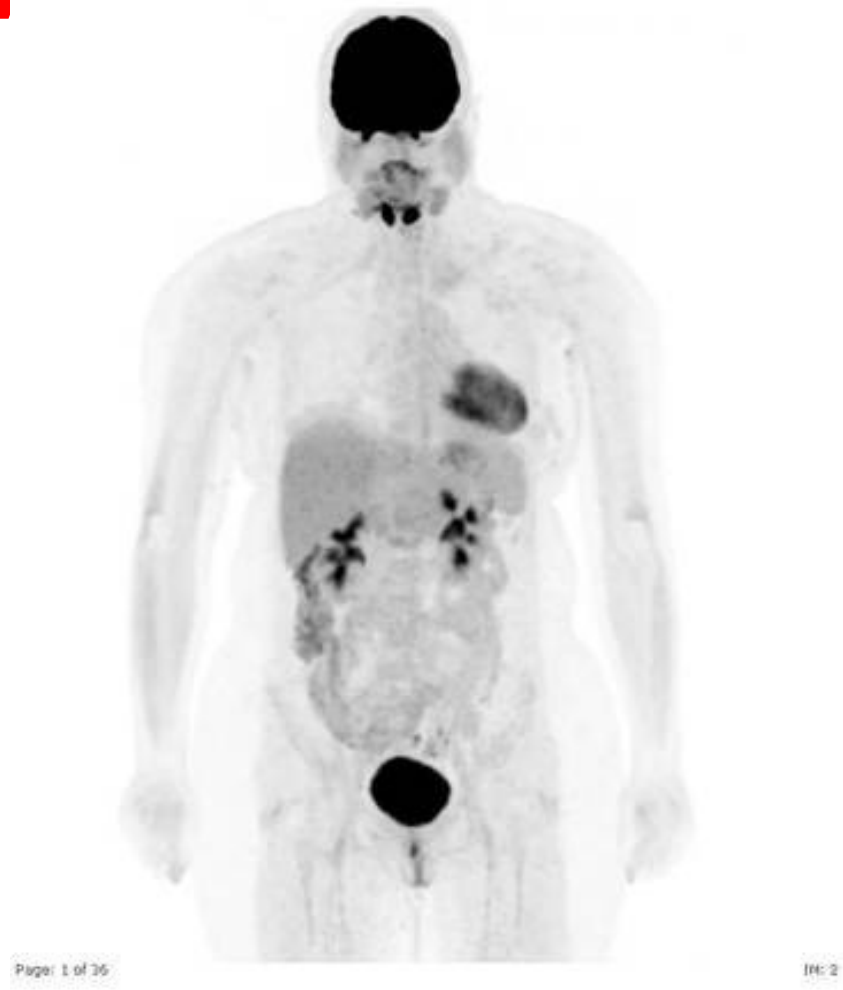

Fever ≥38.3° C (≥101° F) and illness lasting ≥3 weeks and no known immunocompromised state
History and physical examination
Stop antibiotic treatment and glucocorticoids
Obligatory investigations:
ESR or CRP, hemoglobin, platelet count, leukocyte count and differential, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, AST, ALT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n = 3), urine culture, chest x-ray, abdominal ultrasonography, and tuberculin skin test or IGRA
Exclude manipulation with thermometer
Stop or replace medication to exclude drug fever
PDCs present
PDCs absent or misleading
Guided diagnostic tests
Cryoglobulin and funduscopy
DIAGNOSIS
NO DIAGNOSIS
FDG-PET/CT (or labeled leukocyte scintigraphy or gallium scan); see Fig. 17-2
Scintigraphy abnormal
Scintigraphy normal
Confirmation of abnormality (e.g., biopsy, culture)
Repeat history and physical examination
Perform PDC-driven invasive testing
DIAGNOSIS
NO DIAGNOSIS
DIAGNOSIS
NO DIAGNOSIS
Chest and abdominal CT
Temporal artery biopsy (≥55 years)
DIAGNOSIS
NO DIAGNOSIS
Stable condition:
Follow-up for new PDCs
Consider NSAID treatment
Deterioration:
Further diagnostic tests
Consider therapeutic trial

FLUORODEOXYGLUCOSE PET/CT

- FDG PET/CT has become an established imaging procedure in FUO
- **Mechanism** : FDG accumulates in Tissue with high Glycolysis rate like malignant cells and activated leucocytes
- **Advantages**: High resolution, greater sensitivity and high accuracy
- **Physiological uptake**: brain , heart, bowl , kidney and bladder
- In periodic fevers, correct timing of PET/CT increases its diagnostic value
- In case of non availability of PET/CT we can do CONVENTIONAL SCINTIGRAPHY

NORMAL PET/CT

LARGE V VASCULITIS



TREATMENT

- Empirical therapeutic trials (should be avoid)
- Antibiotics and Antituberculous therapy:
- Diminish culture positivity
- Considered for hemodynamic instability or neutropenia
- ATT trial
  - TST or IGRA positive , Granulomatous disease present
  - No response after 6 weeks of ATT trial ?
- **Colchicine , NSAID and Glucocorticoids** (FMF, GCA and PMR)
- **Interleukin 1 Inhibition** (Anakinra in FMF, Stills disease and periodic syndrome)

Prognosis

- FUO related mortality rates have continuously declined over recent decades

- Majority of fevers are caused by treatable diseases

Important Points:

Try to find Potentially Diagnostic Clues (PDCs) from history.

Detailed physical examination must be done.

If fever persists beyond 72 hours after discontinuation of suspected drug, it is unlikely that this drug is the cause.

Scintigraphy imaging should only be performed during febrile episode. It will help to identify anatomic location of ongoing metabolic process, and biopsy and cultures can be used to diagnose the disease.


THANK
YOU