PYREXIA OF UNKNOWN ORIGIN

Original Definition

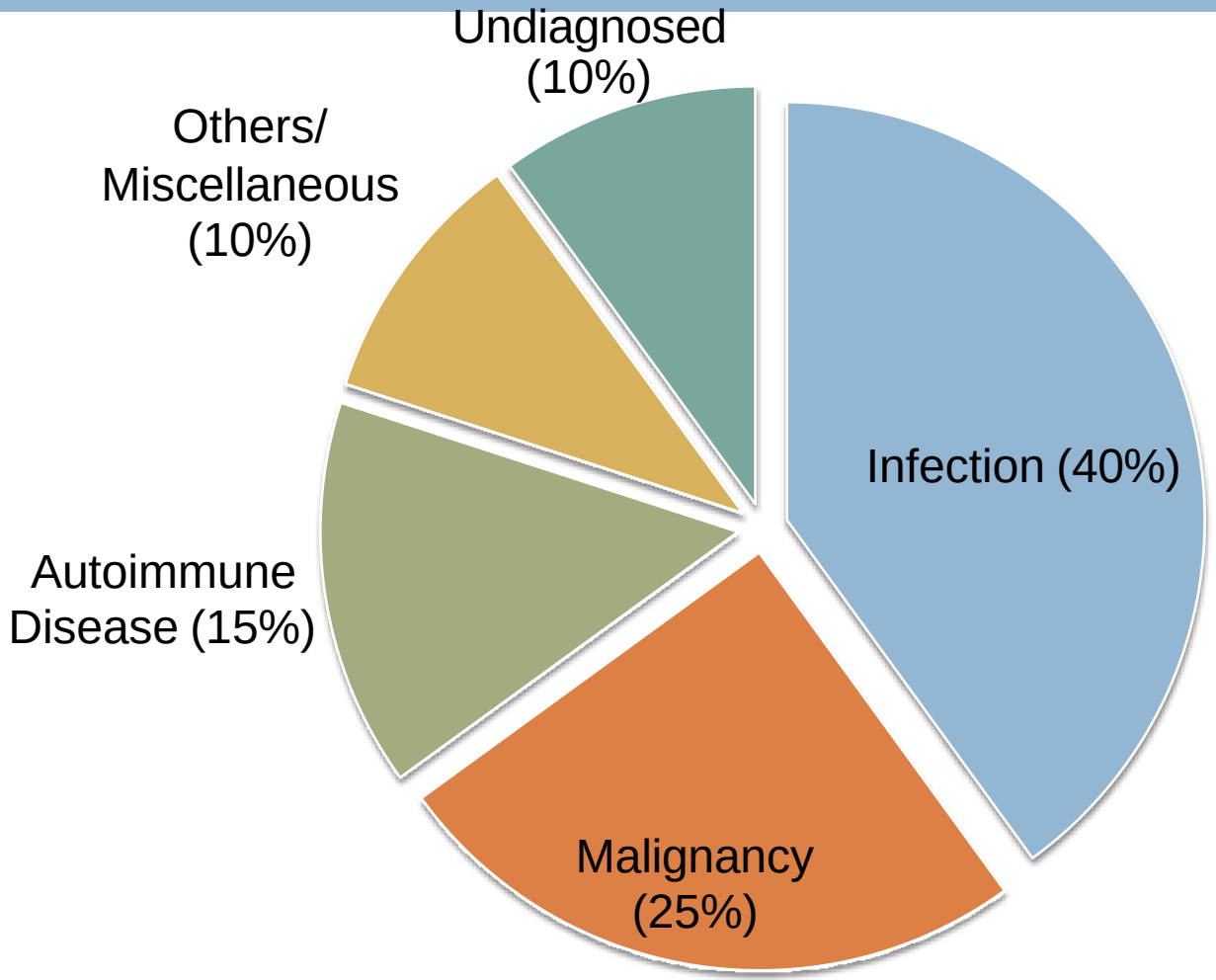
(by *Petersdorf and Beeson, 1961*)

- Temperatures ≥ 38.3ºC (101ºF) on several occasions
- Fever ≥ 3 weeks
- Failure to reach a diagnosis despite 1 week of inpatient investigations or 3 outpatient visits [1 IP / 3 OP]

Classification of PUO

Category	Definition	Aetiologies
Classic	• Temperature >38.3 C (100.9 F) ; • Duration of >3 weeks • Evaluation of at least 3 outpatient visits or 3 days in hospital	• Infection • Malignancy • collagen vascular disease
Nosocomial	• Temperature >38.3 C • Patient hospitalized ≥ 24 hours but no fever or incubating on admission • Evaluation of at least 3 days	• *Clostridium difficile* enterocolitis • drug-induced • pulmonary embolism • septic thrombophlebitis, • sinusitis
Immune deficient (neutropenic)	• Temperature >38.3 C • Neutrophil count ≤ 500 per mm3 • Evaluation of at least 3 days	• Opportunistic bacterial infections, • aspergillosis, • candidiasis, • herpes virus
HIV-associated	• Temperature >38.3 C • Duration of >4 weeks for outpatients, >3 days for inpatients • HIV infection confirmed	• Cytomegalovirus, • *Mycobacterium avium-intracellulare* complex, • *Pneumocystis carinii* pneumonia, • drug-induced, • Kaposi's sarcoma, lymphoma

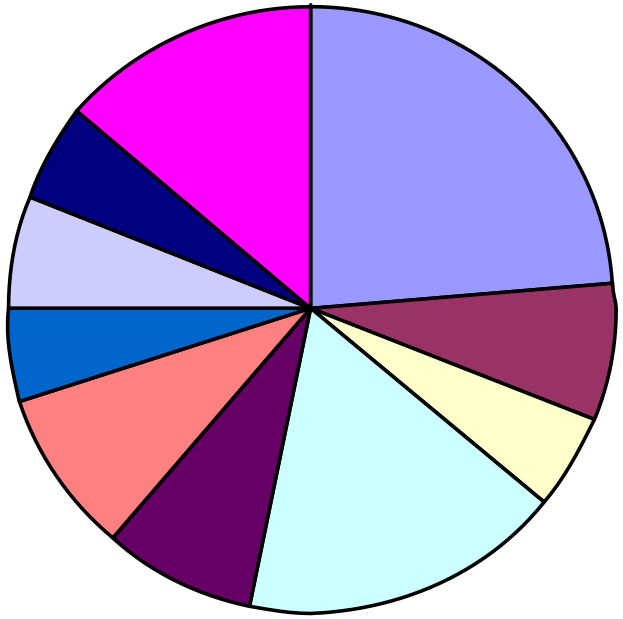
COMMON CAUSES OF PUO



Causes of FUO

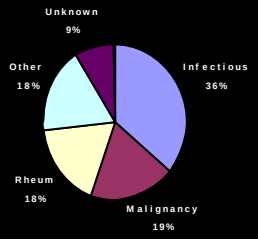
(in India)

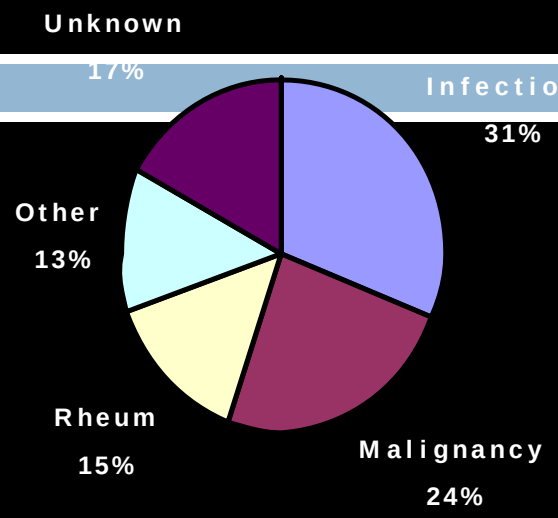
- Infectious 53%
  - #1: TB (45%)
- Neoplasm: 17%
  - #1: NHL (47%)
- Collagen Vasc.: 11%
  - #1 SLE: 45%
- Miscellaneous: 5%
- Undiagnosed: 14%

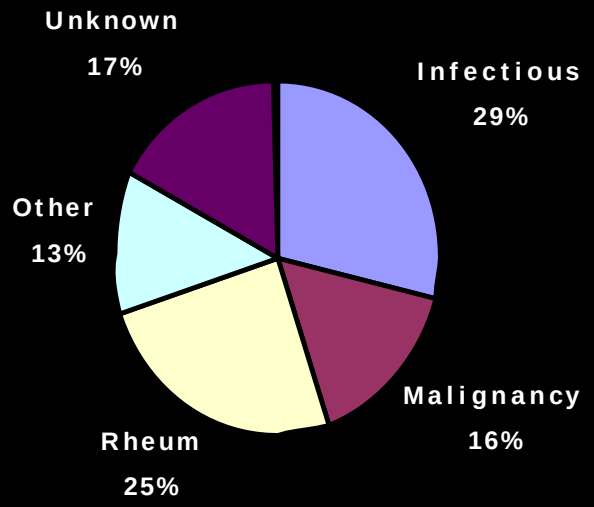


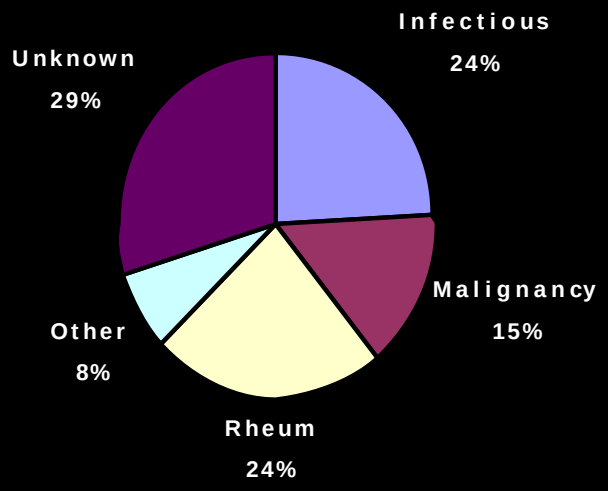
Kejariwal D et al. *J Postgrad Med*. 2001 Apr-Jun; 47(2): 104-7.

FUO by the Decades









Classic PUO

3 common etiologies which account for the majority of classic PUO:

- Infections
- Malignancies
- Collagen Vascular Disease

Others/Miscellaneous which includes drug-induced fever.

Infections

- Bacterial: abscesses, TB, complicated UTI, endocarditis, osteomyelitis, sinusitis, Lyme disease, prostatitis, cholecystitis, empyema, bili ary tract infection, brucellosis, typhoid, leptospirosis, Q fever, borreliosis, etc.
- Parasite: Malaria, toxoplamosis, leishmaniasis, etc.
- Fungal: histoplasmosis, etc.
- Viral: CMV, infectious mononucleosis, HIV, etc.

Infections

- As duration of fever increases, infectious etiology decreases
- Malignancy and factitious fevers are more common in patients with prolonged FUO.

Malignancies

- Haematological
  - Lymphoma
  - Chronic leukemia
- Non-haematological
  - Renal cell cancer
  - Hepatocellular carcinoma
  - Pancreatic cancer
  - Colon cancer
  - Hepatoma
  - Myelodysplastic Syndrome
  - Sarcomas

Collagen vascular disease / Autoimmune disease

- Adult Still's disease
- Polymyalgia rheumatica
- Temporal arteritis
- Rheumatoid arthritis
- Rheumatoid fever
- Inflammatory bowel disease
- Reiter's syndrome
- Systemic lupus erythematosus
- Vasculitides
- Polyarteritis nodosa
- Giant cell arteritis
- Kawasaki disease
- Still’s disease

Others/miscellaneous

- Drugs:
  penicilin, phenytoin, captopril, allopurinol, eryth romycin, cimetidine, etc.
- Hyperthyroidism
- Alcoholic hepatitis
- Sarcoidosis
- Inflammatory bowel disease
- Deep Venous Thrombosis

TABLE 3

Agents Commonly Associated with Drug-Induced Fever

Allopurinol (Zyloprim)
Captopril (Capoten)
Cimetidine (Tagamet)
Clofibrate (Atromid-S)
Erythromycin
Heparin
Hydralazine (Apresoline)
Hydrochlorothiazide (Esidrix)
Isoniazid
Meperidine (Demerol)
Methyldopa (Aldomet)
Nifedipine (Procardia)
Nitrofurantoin (Furadantin)
Penicillin
Phenytoin (Dilantin)
Procainamide (Pronestyl)
Quinidine

Roth AR and Basello GM. *Am Fam Physician*. 2003 Dec 1;68(11):2223-8.

Nosocomial PUO

- More than 50% of patients with nosocomial PUO are due to infection.
- Focus on sites where occult infections may be sequestered, such as:
  - Sinusitis of patients with NG or oro-tracheal tubes.
  - Prostatic abscess in a man with a urinary catheter.
- 25% of non-infectious cause includes:
  - Acalculous cholecystitis,
  - Deep vein thrombophlebitis
  - Pulmonary embolism.

Neutropenic PUO

- Patients on chemotherapy or immune deficiencies are susceptible to:
  - Opportunistic bacterial infection
  - Fungal infections such as candidiasis
  - Bacteremic infections
  - Infections involving catheters
  - Perianal infections.
- Examples of aetiological agent:
  - aspergillus
  - Candida
  - CMV
  - Herpes simplex

HIV-associated PUO

- HIV infection alone may be a cause of fever.
- Common secondary causes include:
  - Tuberculosis
  - Toxoplasmosis
  - CMV infection
  - P. carinii infection
  - Salmonellosis
  - Cryptococcosis
  - Histoplasmosis
  - Non-Hodgkin's lymphoma
  - Drug-induced fever

Pyrexia of Unknown Origin

A Clinical Approach

History Taking

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
  - Saddleback fever: Leptospirosis, dengue,borrelia
- -relapsing/ recurrent fever: Non-falciparum malaria, Brucellosis, Hodgkin's lymphoma

4。Antecedents

- prior to onset of fever:
  - dental extraction: Infective endocarditis
  - Urinary catherization: UTI, bacteremia.

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
- Joint pain
  - RA, SLE, vasculitis

- Abd. Pain
  - Cholangitis, biliary obstruction, perinephric abscess, Crohn's disease, dissecting aneuryms, gynaecological infection
- Bone pain
  - Osteomyelitis, lymphoma
- Sorethroat
  - IM, retropharyngeal abscess, post-Streptococcal infection
- Dysuria, rectal pain
  - Prostatic abscess, UTI
- Altered bowel habit
  - IBD, thyphoid fever, schistosomiasis, amoebiasis
- Skin rash
  - Gonococcal infection, PAN, NHL, dengue fever

- Past Medical History
  - Malignancy = leukemia, lymphoma, hepatocellular ca
  - HIV infection
  - DM
  - IBD
  - collagen vascular disease-SLE, RA, giant cell arteritis
  - TB
  - Heart disease: valvular heart disease
- Past Surgical History
  - Post splenectomy/ post- transplantation
  - Prosthetic heart valve
  - Catheter, AV fistula
  - Recent surgery/ operation

- Drug History
  - Immunosuppressive drug/ corticosteroid
  - Anticoagulants: accumulation of old blood in closed space e.g. retroperitoneal, perisplenic
  - Before fever: **drug fever** →occur within 3 months after starting taking drugs
    - may cause hypersensitivity and low grade fever, usually associated with rash
    - Due to the allergic reaction, direct effect of drug which impair temperature regulation (e.g. phenothiazine)
    - E.g. Antiarrhythmic drug: procainamide, quinidine; Antimicrobacterial agent: penicillin, cephalosporin, hydralazine
  - After fever: may modify clinical pictures, mask certain infection e.g. SBE, antibiotic allergy
- Family History
  - Anyone in family has similar problem: TB, familial Mediterranian fever

- Social History
  - Travel
    - amoebiasis, typhoid fever, malaria, Schistosomiasis
  - Residental area
    - malaria, leptospirosis, brucellosis
  - Occupation
    - farmers, veterinarian, slaughter-house workers = Brucellosis
    - workers in the plastic industries = polymer-fume fever
  - Contact with domestic / wild animal / birds :
    - Brucellosis, psittacosis (pigeons), Leptospirosis, Q fever, Toxoplasmosis
  - Diet history
    - unpasteurized milk/cheese = Brucellosis
    - poorly cooked pork = Trichinosis
  - IVDU = HIV-AIDS related condition, endocarditis
  - Sexual orientation = HIV, STD, PID
  - Close contact with TB patients

Pyrexia of Unknown Origin

Physical Examination

Examination

- General
  - Pattern of fever
    (continous, intermittent, relapsing)
  - Ill/not ill
  - Weight loss (chronic illness)
  - Skin rash

Hands

- Stigmata of Infective Endocarditis
- Vasculitis changes
- Clubbing
- Presence of arthropathy
- Raynaud's phenomenon

Arms

- Drug injection sites (ivdu)
- Epitrochlear and axillary nodes (lymphoma, sarcoidosis, focal infection)
- Skin

Head & neck

- Feel temporal arteries (tender & thicken)
- Eyes – iritis/conjuctivitis (ct disease – reiter syndrome)
- Jaundice (ascending cholangitis)
- Fundi – choroidal tubercle (miliary tb), roth's spot (ie) and retinal haemorrhage (leukaemia)
- Lymphadenopathy

Face & mouth

- Butterfly rash
- Mucous membranes
- Seborrhoic dermatitis (hiv)
- Mouth ulcers (sle)
- Buccal candidiasis
- Teeth & tonsils infection (abscess)
- Parotid enlargement
- Ears – otitis media

Chest

- Bony tenderness
- Cvs – murmurs (ie, atrial myxoma), rubs (pericarditis)
- Resp – signs of pneumonia, tb, empyema and lung ca

Abdomen

- Rose coloured spot (typhoid fever)
- Hepatomegaly (sbp, hepatic ca, met)
- Splenomegaly (haemopoietic malignancy, ie, malaria)
- Renal enlargement (renal cell ca)
- Testicular enlargement (seminoma)
- Penis & scrotum – discharge/rash
- Inguinal ligament
- Per rectal exam – mass/tenderness in rectum/pelvis (abscess, ca, prostat itis)
- Vaginal Examination – collection of pelvic pus/ Pelvic Inflammatory Disease

Central Nervous System

- Signs of meningism (chronic tb meningitis)
- Focal neurological signs (brain abscess, mononeuritis multiplex in polyarteritis nodosa)

Pyrexia of Unknown Origin

Investigation

Stage 1: Laboratory investigations

Stage 1: (screening tests)

1. Full blood count
2. ESR & CRP
3. BUSE
4. LFTs
5. Blood culture
6. Serum virology
7. Urinalysis and culture
8. Sputum culture and sensitivity
9. Stool FEME and occult blood
10. CXR
11. Mantoux test

Stage 2: Laboratory investigations

Stage 2:

1. Repeat history and examination
2. Protein electrophoresis
3. CT (chest, abdomen, pelvis)
4. Autoantibody screen (ANA, RF, ANCA, anti-dsDNA)
5. ECG
6. Bone marrow examination
7. Lumbar puncture
8. Consider PSA, CEA
9. Temporal artery biopsy
10. HIV test counselling

Stage 3: Laboratory investigations

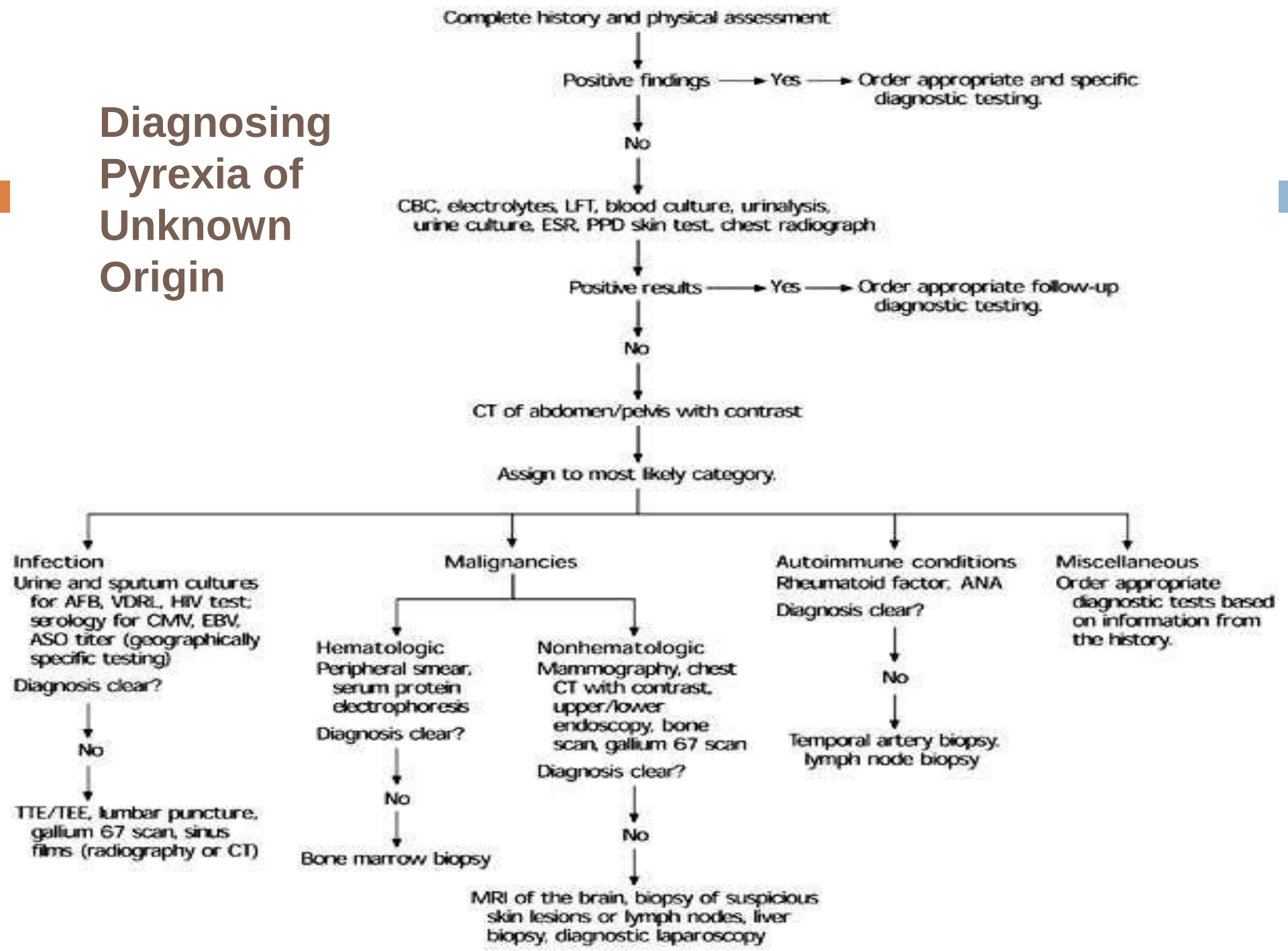
Stage 3:

1. Echocardiography
2. Further Ix abdomen (Indium-labelled WC scan – IBD, abscesses, local sepsis)
3. Barium studies
4. IVU
5. Liver biopsy
6. Exploratory laparotomy
7. Bronchoscopy

Stage 4: Laboratory investigations

- Treat TB,
- endocarditis,
- vasculitis,
- trial of aspirin/ steroids

Diagnosing Pyrexia of Unknown Origin



Imaging Studies

Chest radiograph	• Tuberculosis, malignancy, *Pneumocystis carinii* pneumonia
CT of abdomen or pelvis with contrast agent	• Abscess, malignancy
Gallium 67 scan	• Infection, malignancy
Indium-labeled leukocytes	• Occult septicemia
Technetium Tc 99m	• Acute infection and inflammation of bones and soft tissue
MRI of brain	• Malignancy, autoimmune conditions
PET scan	• Malignancy, inflammation
Transthoracic or transesophageal echocardiography	• Bacterial endocarditis
Venous Doppler study	• Venous thrombosis

Diagnosis

- More invasive testing, such as LP or biopsy of bone marrow, liver, or lymph nodes, should be performed only when clinical suspicion shows that these tests are indicated or when the source of the fever remains unidentified after extensive evaluation.
- When the definitive diagnosis remains elusive and the complexity of the case increases, an infectious disease, rheumatology, or oncology consultation may be helpful.