Fever of Unknown Origin

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definition

- 1961- FUO was seen as temperature >38.3C on several occasions, fever >3 weeks duration, and with >1 week of inpatient investigation
- Now:
  - Classic FUO
  - Nosocomial FUO
  - Neutropenic FUO
  - FUO associated with HIV

Classic FUO

- >38.3 C
- 3 outpatient visits or
- 3 days in hospital or
- 1 week of “intelligent and invasive” ambulatory investigation

Nosocomial FUO

- >38.3 C (101 F) develops on several occasions in hospital patient
- No infection on admission
- 3 days of investigation and >2 days incubation of culture

Neutropenic FUO

- >38.3 C on several occasions
- Neutrophil count < 500/ µL
- 3 days investigation
- More than 2 days incubation of culture

FUO associated with HIV

- 38.3 C for > 4wks outpatient, >3 days hospital
- HIV
- 3 days investigations, >2 day cultures

Causes of Classic FUO

1961

- Infections: 36%
- Neoplasms: 19%
- Inflammatory:19%
- Miscellaneous: 19%
- Undiagnosed: 7%

2007

- Infections: 16%
- Neoplasms: 7%
- Inflammatory: 22%
- Miscellaneous: 4%
- Undiagnosed: 51%

For a full list of causes of FUO, please turn to table 18-2 in Harrison's

Infections
Localized pyogenic infections
- Appendicitis
- Cat-scratch disease
- Cholangitis
- Cholecystitis
- Dental abscess
- Diverticulitis/abscess
- Lesser sac abscess
- Liver abscess
- Mesenteric lymphadenitis
- Osteomyelitis
- Pancreatic abscess
- Pelvic inflammatory disease
- Perinephric/intrarenal abscess
- Prostatic abscess
- Renal malacoplakia
- Sinusitis
- Subphrenic abscess
- Suppurative thrombophlebitis
- Tuboovarian abscess

Intravascular infections
- Bacterial aortitis
- Bacterial endocarditis
- Vascular catheter infection

Systemic bacterial infections
- Bartonellosis
- Brucellosis
- *Campylobacter* infection
- Cat-scratch disease/bacillary angiomatosis (*B. henselae*)
- Gonococcemia
- Legionnaires' disease
- Leptospirosis
- Listeriosis
- Lyme disease
- Melioidosis
- Meningococcemia
- Rat-bite fever
- Relapsing fever
- Salmonellosis
- Syphilis
- Tularemia
- Typhoid fever
- Vibriosis
- *Yersinia* infection

Infections

1. Extrapulmonary TB, typhoid, Malaria
2. Delayed Antibody response to EBV, CMV, HIV
3. Intra-abdominal abscesses- difficult
4. Renal malacoplakia→ life threatening
5. Osteomyelitis- especially if prosthetic devices
6. Endocarditis by HACEK

Infections

- Fungal diseases and protozoa
  - Histoplasmosis
  - Aspergillosis
  - Pneumocystis infection
  - If have headache→ CSF culture for cryptococcus neoformans, M. Tuberculosis

Inflammatory

- Polymyalgia Rheumatica
- Lupus
- Adult Still's
- Sarcoidosis
- Crohn's
- Granulomatous hepatitis

In the elderly

1. Giant Cell arteritis (15-20%)
2. Tuberculosis
3. Colon cancer

Miscellaneous

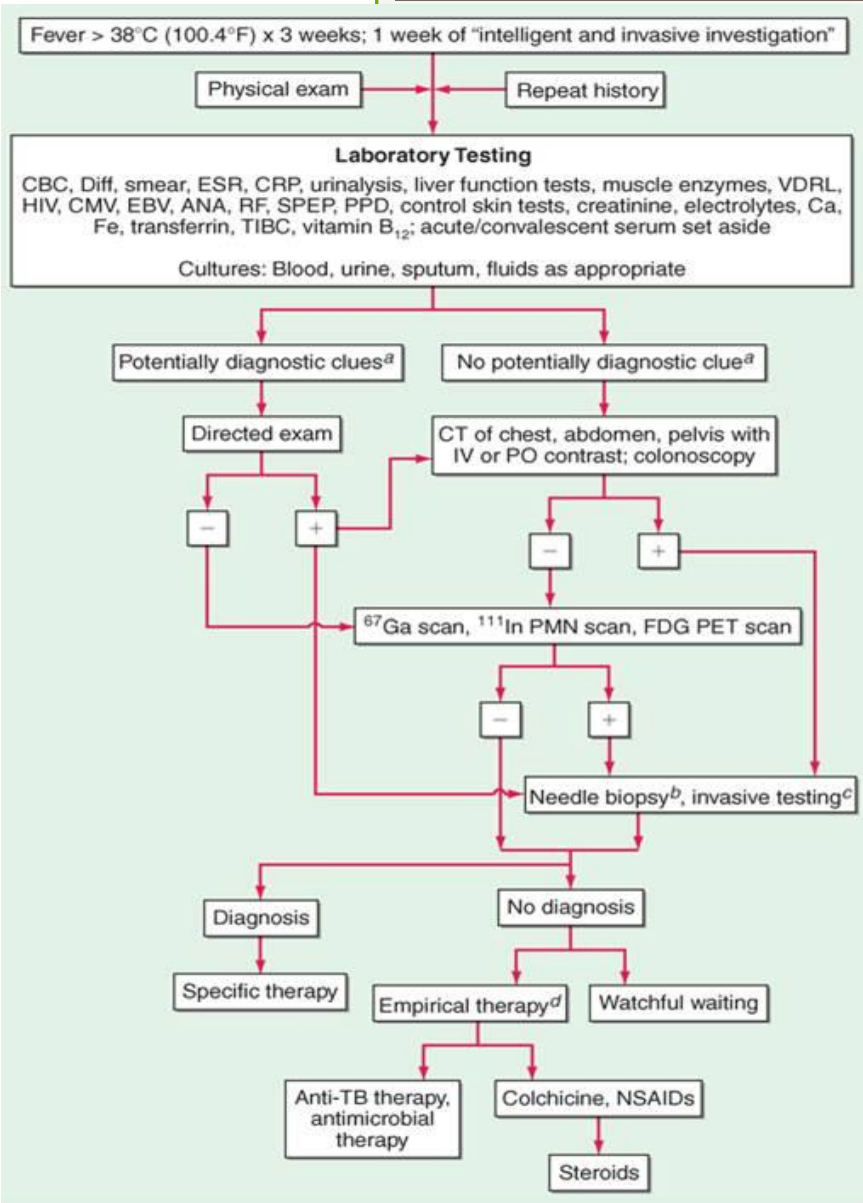
- Drug induced fever
- PE
- Factitious fever (esp. young women in health professions)
- Hereditary periodic fever (FMF, hyper IgD, familial Hiberian fever)
- Familial cold urticaria
- Fabry, Gaucher's
- Thermoregulatory disorders (pheochromocytoma, hypothalamic dysfucntion etc)

Drug- induced fever

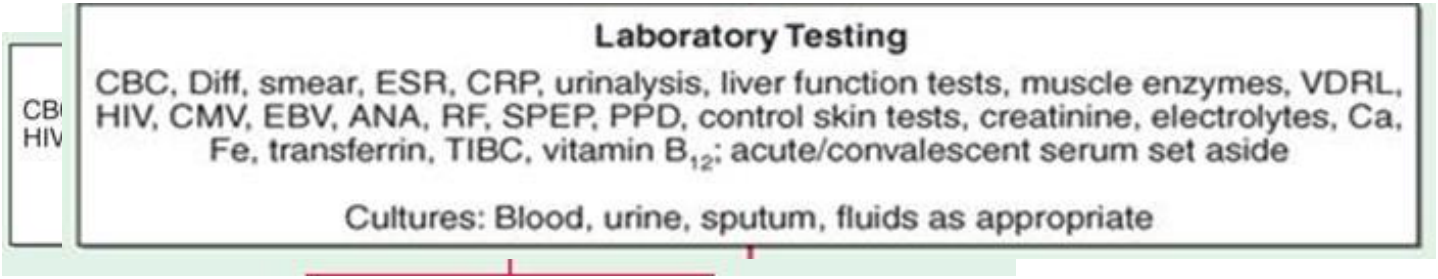
- Antibiotics
  - β lactams
- Cardiovascular drugs (ex. Quinidine)
- Antineoplastic drugs
- Drugs acting on CNS (ex. Phenytoin)

Diagnosis- things to consider

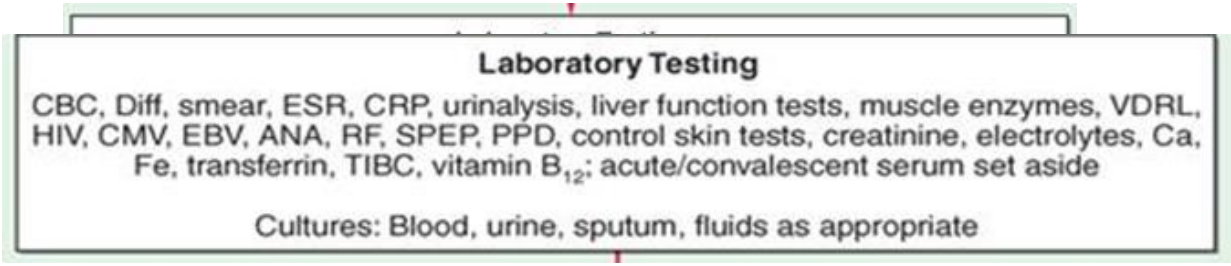
- Patient's country of origin
- Recent and remote travel
- Environmental exposures
- Pets
- Immunosuppression, disease- modifying interventions (TNF-a suppression)
  - Can hide infections or make old ones reappear



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com



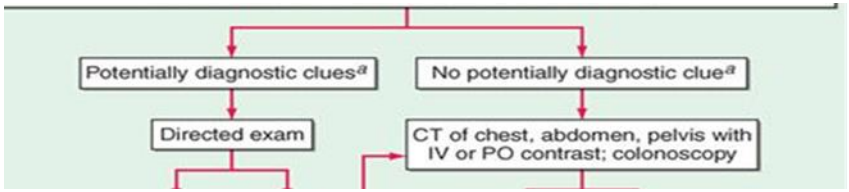
- Elevated ESR + anemia→ giant cell arteritis, polymyalgia rheymatica
- Elevated ESR, leukocytosis, anemia, arthralgia, polyserositis, lymphadenopathy, splenomegaly, rash → Still's disease
- CRP can be used as cross-reference for ESR
- Elevated ACE→ sarcoidosis?



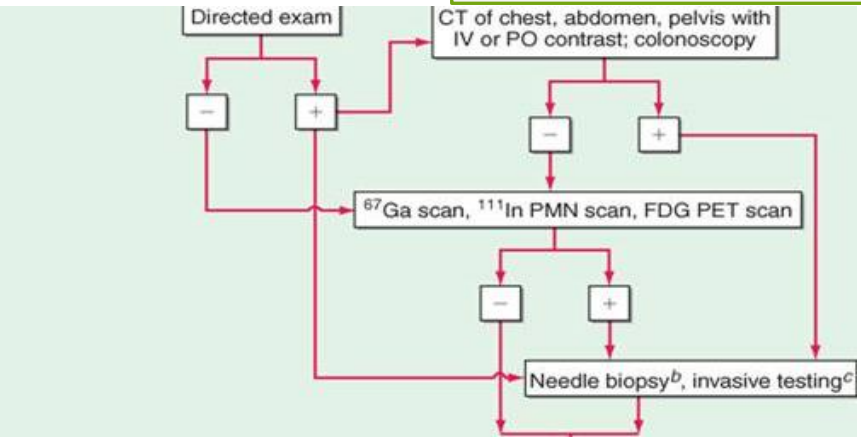
- Need specialized media if travel history suggests uncommon causes of endocarditis (Histoplasma, Chlamydophila, Mycoplasma, Bartonella etc)
- Cultures positive for multiple organisms can indicate self- injection
- VDRL= venereal diseases research lab test

For infections- new development

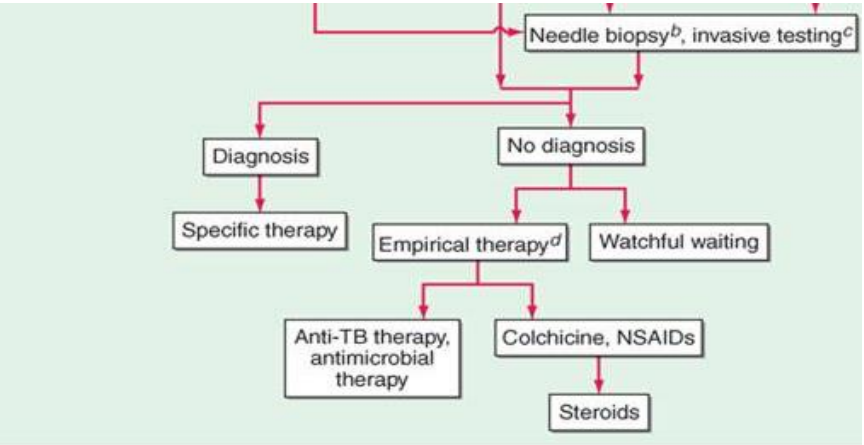
- Use of microarray (with PCR) containing probes of
  - all recognized virus species hosted by vertebrates
  - 135 bacterial species
  - 73 fungal species
  - 63 parasite species



- Potentially diagnostic clues= de Klein et al for key findings in history, localizing signs, key symptoms
- CXR if new symptoms
- If pulmonary signs→ sputum induced and bronchoalveolar lavage
- MRI better at detecting spinal/ paraspinal lesion, abscesses, aortic dissection
- Upper GI endoscopy with contrast + colonoscopy (especially in elderly)



- Prolonged fever→ liver, bone marrow biopsy
  - Look for bacteria, mycobacteria, fungi
- ^{67} Ga useful in localizing inflammatory process
  - Crohn's, sarcoidosis



- Empirical therapy is last resort.
- Most patients with FUO have a good prognosis without a diagnosis
- Exploratory laparotomy is also done as final measure, but now has been replaced with more imaging techniques

Treatment- Classic FUO

- Consider empirical early on in the elderly
- Avoid empirical therapy unless vital sign instability or neutropenia
  - Also consider if there is cirrhosis, asplenia, DMARD use, immunosuppressive drugs, exotic travel
- Continued observation, examination
- Glucocorticoids→ drastic change if temporal arteritis, polymyalgia rheumatica, granulomatous hepatitis
- NSAID→ dramatic change if rheumatic fever or Still's
- Avoid glucocorticoids, NSAID unless rule out infection

Nosocomial FUO

- >50 % are infections
  - IV lines, phlebitis, prostheses
  - C. Difficile
- Focus on sites where may be infected
- 25% non-infectious (DVT, PE, Drug, withdrawal, adrenal insufficiency, thyroiditis, pancreatitis, acalculous cholecystitis)
- Accelerated pace of diagnostic test, CT, MRI, USS
- IV lines change, drugs stopped for 72 hrs, empirical therapy + vancomycin for MRSA

Neutropenic FUO

- Bacteria, fungal infections
- Bacteremia, catheters, perianal infections
- Candida, Aspergillus→ common
- HSV, CMV
- Extensive guidelines
- Vancomycin + ceftazimide, cefepine or carbapenem, +/- aminoglycoside

HIV associated FUO

- HIV alone can cause fever
- Blood cultures, CXR, biopsy, serologic studies (cryptococcal antigen)
- Myc. Avium, M. intracellulare, TB, toxoplasmosis, CMV, Pneumocystitis, nonhodgkin lymphoma, drug-induced
- Tx depends on many factors