Fever of Unknown Origin (FUO)

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FUO: patient’s subtypes

- **classical FUO**

- **nosocomial** ~ (hospitalized > 24h, no prior fever)
  - C. difficile, drugs, etc.

- **immune deficient / neutropenic** ~
  (abs. neutrophil count < 500)
  - bacteremia, fungal, HSV, etc.

- **HIV-related** ~
  - opportunistic infections (M. avium, CMV), lymphomas, Kaposi’s, drugs, etc.
“Classical” FUO definition
(Petersdorf and Beeson, 1961)

- fever > 38.3 C, on several occasions
- duration > 3 weeks
- failure to reach diagnosis after
  - 1 week of inpatient investigation  or
  - at least 3 outpatient visits (refined definition)
Differential Diagnosis

- infections
- malignancies MAJOR
- autoimmune diseases
- miscellaneous
  - drugs
  - hepatitis MINOR
  - DVT
  - endocrine causes
  - factitious of self-induced/provoked fever
Frequency base on etiology FUO

- Infection (40%)
- Malignancy (25%)
- Autoimmune Disease (15%)
- Others/Miscellaneous (10%)
- Undiagnosed (10%)
Classic FUO: etiology and epidemiology

- **Infections**: most common! accounting for 1/3 of cases
  - Tuberculosis: most common infection in non-elderly adults
  - PPD pos. < 50% of pts with TB and FUO, sputum samples pos. ¼ of patients
  - Abscesses
    - usually in abdomen or pelvis with some pre-disposing cause (e.g. recent surgery, diab., biliary tract disease, etc.)
  - other infections: osteomyelitis, endocarditis (e.g. in pts with recent antibiotic use)

- **Malignancies**: second most common
  - lymphomas (mainly NHLs), leukemias, renal cell cc., HCC, liver metastasis

- **Autoimmune conditions**: third most common
  - Adult Still’s disease in younger patients; giant cell arteritis in older patients
Diagnostic approaches

- History
  - travel
  - exposures to toxins, sick persons, animals
  - immunosuppression
  - localized symptoms
  - subtle findings? (e.g. jaw claudication, skin symptoms…)
- Fever: degree, type of fever curve, apparent toxicity, and response to antipyretics: not specific enough to guide management!
- Repeated physical examinations
- Careful attention (!) to skin, mucous membranes, lymph nodes, joints, and abdomen
Laboratory investigations

- Suggested minimal diagnostic work-up
  - CBC and differential
  - routine chemistry: LDH, Sebi, liver enzymes
  - We, CRP
  - urine analysis
  - blood, urine culture
  - ANA, RH factor
  - HIV
  - CMV, EBV
  - serologic tests: Q-fever, hepatitis, etc.
- **CT, MRI, PET**
- **Nuclear imaging**
  - for localizing inflammatory or infectious foci
    - Tc99-scans: spec. 93%, sens. 40-75%
    - Indium-labeled WBC scans: spec. 69%-86%, sens. 45%-82%
- **Ga67-scans**
- **TTE, TEE**
- Temporal artery biopsy
  - Arteritis: ~16% of FUO pts
- Leg Doppler-USG
  - DVT: 2-6% of FUO pts
- Liver biopsy
  - Diagnostic yield: 14%-17% regardless of whether abnormal physical exam or liver enzymes exist
- Bone marrow examination
  - Not recommended in immunocompetent pts
- Abdominal exploration
  - Not recommended (CT, MRI, etc. !)
- Empiric therapy (antibiotics, anti-TB, corticosteroids)
  - Not recommended
## Infections

### Viral
- Rhinovirus, adenovirus
- Parainfluenza
- Enterovirus, ECHO
- Influenza
- EBV, CMV
- Colorado tick fever

### Bacterial
- Staphylococcus aureus
- Listeria monocytogenes
- Salmonella thyphi, S. parathyphi
- Streptococci

### Animal exposure
- Coxiella burneti (Q fever)
- Leptospirosas
- Brucella species

### Granulomatous infection
- Mycobacterium tuberculosis
- Histoplasma capsulatum
Localized infections

**Most common:** occult abscess (liver, spleen, kidney, brain, bone)

**Less common:**
- cholangitis
- osteomyelitis
- urinary tract infection
- paranasal sinusitis
## Infections: regional lymphadenomegaly

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyogenic</td>
<td>Staph. aureus, Streptococci</td>
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<tr>
<td>Tuberculosis</td>
<td>Scrofula (cervical adenitis)</td>
</tr>
<tr>
<td>Cat-scratch disease</td>
<td>Bartonella</td>
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<tr>
<td>Ulceroglandular fever</td>
<td>Tularemia</td>
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<tr>
<td>Oculoglandular fever</td>
<td>Tularaemia</td>
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<tr>
<td>Inguinal Syphilis, Herpes</td>
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<tr>
<td>Plague</td>
<td>Yersinia</td>
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</tbody>
</table>
Systemic infections

**Most common:** Tuberculosis, endocarditis

**Less common:**
- EBV, CMV
- toxoplasmosis, brucellosis
- Q-fever, cat-scratch disease, malaria
- HIV or opportunistic infections
### Infections: generalized lymphadenomegaly

<table>
<thead>
<tr>
<th>Viral</th>
<th>Measles</th>
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<tbody>
<tr>
<td></td>
<td>Rubella</td>
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<td></td>
<td>Hepatitis B</td>
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<tr>
<td>Bacterial</td>
<td>Scarlet fever</td>
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<td>Brucellosis</td>
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<td>Leptospirosis</td>
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<td></td>
<td>Tuberculosis</td>
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<td>Syphilis</td>
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<td>Lyme disease</td>
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</tbody>
</table>
NEOPLASMS

Most common: NHLs, leukemias

Less common:
- pr. and met. liver tumors
- renal cell carcinomas
- atrial myxoma
- MDS
- colon cancer
- sarcomas
AUTOIMMUNE DISEASES

Most common:
- systemic lupus erythematosus
- juvenile dematomyositis
- juvenile RA
- polyarteritis nodosa

Less common:
- giant cell arteritis
- polymyalgia rheumatica
- adult Still’s
- Behcet’s
MISCELLANEOUS CAUSES

- drug-induced fever
- sarcoidosis
- IBD
- Whipple's disease
- familial Mediterranean fever
- recurrent pulmonary emboli
- alcoholic hepatitis
- thyroiditis
- diabetes insipidus
- Castleman’s disease
- factitious fever
<table>
<thead>
<tr>
<th>Agents Commonly Associated with Drug-Induced Fever</th>
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<tbody>
<tr>
<td>Allopurinol (Zyloprim)</td>
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<tr>
<td>Captopril (Capoten)</td>
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<tr>
<td>Cimetidine (Tagamet)</td>
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<tr>
<td>Clofibrate (Atromid-S)</td>
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<tr>
<td>Erythromycin</td>
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<tr>
<td>Heparin</td>
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<tr>
<td>Hydralazine (Apresoline)</td>
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<tr>
<td>Hydrochlorothiazide (Esidrix)</td>
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<tr>
<td>Isoniazid</td>
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<td>Meperidine (Demerol)</td>
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<tr>
<td>Methyldopa (Aldomet)</td>
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<tr>
<td>Nifedipine (Procardia)</td>
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<td>Nitrofurantoin (Furadantin)</td>
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<td>Penicillin</td>
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<tr>
<td>Phenytoin (Dilantin)</td>
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<td>Procainamide (Pronestyl)</td>
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<td>Quinidine</td>
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