Fever

- **Normal body temperature:**
  - 37°C (set point)
  - Circadian variation <1°C: 36.3 - 37.2°C
  - rectal T 0.4°C > oral T 0.4°C > axillary T

- **Definition of fever:**
  - An elevation of core body temperature above the normal range
Fever (with pyrogens)

Pyrogens

Elevated set-point

Maintaining an abnormally elevated Temperature

BMR (basal metabolic rate) increases

BMR ↑ 10% = T ↑ 0.6°C

T ↑ = Elevated set-point
PATHOGENESIS OF FEVER

- Bacteria and bacterial products
- Viruses
- Crystals (e.g., urate)
- Antigen antibody complex
- Antigens
- T-lymphocyte
- Lymphokines
- Endogenous pyrogens (interleukin 1) (Tumor necrosis factor) (Interferon α)

HYPOTHALAMUS

- Prostaglandin E
- Increase in body temperature
  - "set point"
  - Heat generation
  - Heat conservation
  - Fever
**Fever**

- ExP ➔ Macrophage lymphocyte ➔ EnP ➔ hypothalamus
- Heat production ➔ Set point ➔ Heat loss ➔ Fever ➔ Heat production ➔ Set point ➔ Heat loss ➔ Fever

**Set point**

- Heat production
- Heat loss

**Fever**

- ExP ➔ Macrophage lymphocyte ➔ EnP ➔ hypothalamus
- Heat production ➔ Set point ➔ Heat loss ➔ Fever ➔ Heat production ➔ Set point ➔ Heat loss ➔ Fever
FEVER (without pyrogens)

Excessive heat production

Decreased dissipation

Loss of regulation

$T \uparrow > \text{unchanged set-point}$
ACUTE FEBRILE ILLNESS

- always represents a common problem
- Acute onset with localizing symptoms
  --------easy to get diagnosis
- gradual onset without toxic
  ------only need follow-up are required
- gradual onset with toxic
  ------hospitalization should be considered
FEVER OF UNKNOWN ORIGIN

- **Old Definition:**
  1. Fever higher than 38.3°C on several occasions.
  2. Duration of fever – 3 weeks
  3. Uncertain diagnosis after one week of study in hospital

- **New Definition:**
  - Eliminated the in-hospital evaluation requirements → 3 outpatient visits, or 3 days in hospital. ... Ambulatory as well as in hospital
Epidemiology and Etiology

**Categories of Illness Causing PUO**

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>30 - 40 %</td>
</tr>
<tr>
<td>Malignancies</td>
<td>20 – 25 %</td>
</tr>
<tr>
<td>Collagen Vascular Disease</td>
<td>25 – 30 %</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>10 – 15 %</td>
</tr>
</tbody>
</table>
The Age

- **Children →** infection is the most frequent.
  - EBV, CMV… others

- **Elderly →** Neoplasm & CT-Disorders
  - Giant cell arteritis } > 50 yr (30%)
  - Polymyalgia Rheumatica }
Etiologies of FUO

- **Infection**
  - Tuberculosis: Disseminated
    - Usually extrapulmonary
    - Occurs in the lungs and significant pre-existing lung disease.
    - Pulmonary TB in AIDS is often subtle (normal chest x-rays → 15 – 30%).
    - PPD (+) < 50% of TB with PUO.
    - Diagnosis often requires Bx of LN/Liver/Bone marrow.
    - Sputum smear (+) only 25%
    - Clinic: various
Tuberculous brain abscesses

Disseminated blood type lung tuberculosis

tuberculous lymphadenitis

Skin tuberculosis
Etiologies of FUO

- Abscess:
  - Usually located in abdomen or pelvis.
  - Secondary to appendicitis or diverticulitis.
  - Pyogenic liver abscess usually follow biliary tract dis./abd. Suppuration.
  - Amoebic liver abscess is similar to pyogenic → amoebic serology is positive > 95% of cases.
  - Splenic abscess is usually secondary to hematogenous seeding.
  - Perinephric or renal abscess is usually secondary to UTI.
Etiologies of PUO

- **Bacterial Endocarditis**
  - Culture remains negative in 5% of patient.
  - Culture negative is likely with the following organisms:
    - Coxiella burnetii → no growth.
    - HACEK group → incubate blood 7 – 21 days
    - Brucella } Special media/
    - Legionella } long time
    - Mycoplasma/Chlamydia }
    - Fungal → usually sterile
  - Peripheral signs may not be detected.
  - Right-side Endocarditis → Lack murmurs → self antibiotics → growth (-ve).
Etiologies of FUO—Malignancy

- **Lymphoma:**
  - Fever is a well-recognized manifestation.
  - Pel-Ebstein phenomenon.
  - Source of fever → production of cytokines.
  - Fever is a negative prognostic factor …

- **Renal Cell Carcinoma (Adult)**
  - 20% → Fever
  - Microscopic hematuria/Erythromyelosis
Etiologies of FUO

- Collagen-Vascular-Disease
  - No diagnostic serology…
  - You need to recognize the syndrome otherwise no diagnosis
  - Still’s disease (young or adult)
  - SLE
  - Giant cell arteritis → 15% of PUO
  - Polymyalgia Rheumatica }
  - Behcet’s Disease
  - Relapsing polychondritis
Etiologies of FUO

- Still’s Disease Adult Onset
  - 16 – 33 % without RF & ANA
  - Fever is high and spiking with Temp up to 41.6°C
  - Fever is either intermittent or remittent …
    peaks typically at night
  - Most patient seek medical attention within 2 weeks.
  - A distinctive evanescent macular or other rash is typically present during the course of the illness.
Still’s Disease
Etiologies of FUO

- **Temporal Arteritis:**
  
  Very serious condition if not diagnosed early
  
  … Very difficult to establish the etiology of fever if you do not have the index of suspicion
  
  Typically Caucasian but it occurs in others
  
  - Fever and malaise may be the only manifestation. Headache is the most common.
Etiologies of PUO

- Careful Questioning → jaw claudication or visual loss.
- If there is unexplained fever, anaemia and high ESR in an elderly without an obvious cause ...
- Unilateral vs. bilateral ... short vs long segment ..
- Treat for 2 years ..
Etiologies of FUO

- **Polymyalgia Rheumatica:**
  - Can cause fever, arthralgia, myalgia & ↑ ESR > 50.
  - Chx. Muscle complaints → symmetrical pain and stiffness that are typically worse at AM and affects lumbar spine and large proximal m.

- **Other vasculitides that cause FUO:**
  - Polyarteritis nodosa → Mononeuritis multiplex (60%)
  - Wegener’s Granulomatosis
  - Mixed Cryoglobulinemia
Etiologies of FUO

- Hyperthyroidism
  - Occasionally cause FUO → most frequently diagnosed clinically.
  - Often accompanied by weight loss.
  - No local neck pain and typically enlarged non-tender thyroid.
PART 2

DIAGNOSIS AND TREATMENT
Diagnostic Approach

- Careful History
- Physical Examination (repeated)
- Diagnostic Testing
History

- **Verify the presence of fever:**
  - Series of 347 patients → for prolonged fever
    → 35% were ultimately: a. No fever
    b. Factitious Fever

- **Duration of Fever:**
  - The longer the duration → the less likely to have infection and malignancy.
History

- **Travel:**
  - Travel to an area known to be endemic for certain disease:
    - Name of the area, duration of stay
    - Onset of illness … (incubation period)

<table>
<thead>
<tr>
<th>1 – 10 Days</th>
<th>10 – 21 Days</th>
<th>Weeks - Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Malaria</td>
<td>Kala Azar</td>
</tr>
<tr>
<td>Plague</td>
<td>Typhoid</td>
<td>Amoebiasis</td>
</tr>
<tr>
<td>Dengue</td>
<td>Brucella</td>
<td>HIV</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Hepatitis A</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>
History

Drug and Toxin History:
- Drug-induced fever ... almost all drug can cause drug fever ... Antihistamine/beta lactam/hepatrin/coumarin/anti-TB ... Salicylates and other NSAID ...
- Alcohol Intake (regular use)
## History

**Localizing Symptoms:**

- May Indicate the source of fever:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back Pain</td>
<td>TB Spondylitis</td>
</tr>
<tr>
<td></td>
<td>Bone Metastasis</td>
</tr>
<tr>
<td>Headache</td>
<td>Chronic Meningitis/GCA</td>
</tr>
<tr>
<td>RUQ Pain</td>
<td>Liver Abscess</td>
</tr>
<tr>
<td>LUQ Pain</td>
<td>Splenic Abscess</td>
</tr>
<tr>
<td>Oral &amp; Genital Ulcer</td>
<td>Behcet’s Disease</td>
</tr>
<tr>
<td>Jaw Claudication</td>
<td>Temporal Arteritis</td>
</tr>
<tr>
<td>Subtle changes in behavior</td>
<td>Granulomatous Meningitis</td>
</tr>
</tbody>
</table>
History

- **Family History:**
  - Scrutinized for possible infectious or hereditary disorders
    - Tuberculosis
    - FMF

- **Past Medical Condition:**
  - Lymphoma → may recur
  - Rheumatic Fever → may recur
  - Still’s Disease → may recur
  - Behcet’s Disease → may recur

- Exposure to sexual partner … Acute HIV
- Illicit drug abuse (IV) … infective endocarditis, Hepatitis … HIV
Physical Examination

Examine the Skin:

- Rash:
  - SLE ..... All types of rashes is described
  - Still’s Disease Evanescent erythematous rash over the trunk
  - Infectious Mononucleosis … macular rash
  - Infective Endocarditis (Janeway’s lesion)
  - Typhoid Fever … rose spots over abdomen

- Osler’s Nodes: Painful nodule on the pads of toes & fingers → Infective Endocarditis
Embolic Skin Lesions ...  
Janeway Lesion

Conjunctival petechiae in a patient with bacterial endocarditis
治疗前

SLE 皮疹

治疗后
Physical Examination

- Examine for Oral Ulcer
  - SLE
  - Behcet’s Syndrome

- Examine for Arthritis

- Examine the Fundus
  - Roth’s spots (white-centered haemorrhage) → Infective Endocarditis
  - Yellowish-white choroidal lesion → Tuberculosis
  - Choriodoretinitis → Active Toxo or CMV in HIV patient.
Diagnostic Testing

- **Blood Testing**
  - Anti-nuclear Antibodies
  - Rheumatoid Factor
  - CMV Antibody … IgM
  - Heterophile Antibody Test in children and young adult
  - Tuberculin Skin Test … 5 unit ID
  - Thyroid Function Test
  - HIV Screening
Diagnostic Testing

- **Cultures**
  - **Blood**
    - Obtain more than 3 blood cultures from separate venipunctures over 24 hr period if you are suspecting inf. Endocarditis prior antimicrobial use.
    - Incubate the blood for 4 weeks, to detect the presence of SBE & Brucellosis
  - **Sputum: For Tuberculosis**
  - **Any normal sterile:**
    - CSF/urine/pleural or peritoneal fluid
    - Bone marrow aspirate → Tuberculosis/Brucellosis
    - Lymph node Bx → TB
Diagnostic Testing

- Imaging Studies: ... to localize abnormalities for definite tests or treatment

  - Chest x-ray:
    - Military shadows → disseminated tuberculosis
    - Atelectasis
      - ↑ Hemi diaphragm} Abscess
      - Pleural Effusion } 1. Liver
      - 1. Liver
      - 2. Spleen
      - 3. Pancreatic
      - 4. Subphrenic
    - Mediastinal mass → Lymphoma/Tuberculosis/Sarcoid
    - If CXR is (N) → Repeat on weekly basis
Diagnostic Testing

- **CT-Scan → CT scan chest**
  - Mediastinal mass → Tuberculosis/Lymphoma/Sarcoidosis
  - Dorsal Spine → Spondylitis and disc space disease
  - **CT-Scan Abdomen → very effective to visualize**
    - All types of abscesses
    - Retroperitoneal tumor, lymph node or haematoma

- **MRI: spleen, lymph node and the brain**
Diagnostic Testing

- **Laparoscopy**
  - To visualize and biopsy the pathology in the abdomen suggestive of:
    - e.g. Tuberculous peritonitis
    - Peritoneal carcinomatosis

- **Biopsy**
  - Enlarged lymph node
    - Granulomatous disease (Tuberculosis)
    - Metastatic carcinoma
    - Others
Therapeutic Trials

- What is the best therapy for FUO patient?
  - To hold therapeutic trials in the early stage… except in:
    - Patient who is very sick to wait.
    - All tests have failed to uncover the etiology.
Prognosis

- It depends on:
  - Cause of fever
  - Nature of the underlying disease(s) BUT .. Generally poor in:
    - Elderly
    - Neoplasms
  - Diagnostic delay has adverse effect in:
    - Intra Abdominal Infection
    - Miliary Tuberculosis
    - Recurrent Pulmonary Emboli
    - Disseminated Fungal Infection

THANK YOU!!!