

# Fever of unknown origin

Ursula Flückiger  
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## Overview

- Approach to a patient with FUO
- Definition of fever of unknown origin (FUO)
- Changes over time
  
- Imaging
  
- Biopsy
  
- Drug fever
  
- Examples and personal experiences

Fever of unknown origin

**APPROACH TO THE PATIENT WITH FUO  
DEFINITION  
CHANGES OVER TIME**

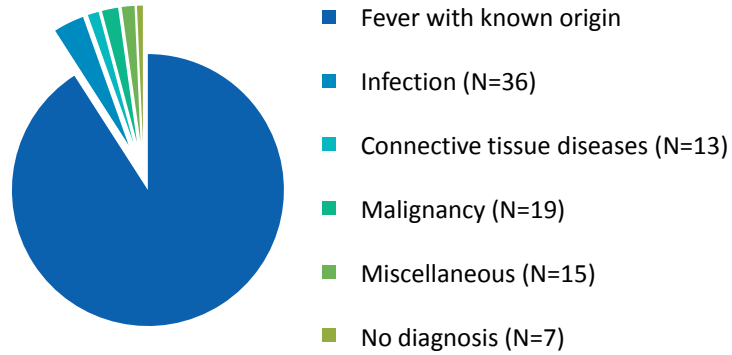
**Patient with fever**

- History and physical examination
- Complete blood count, including differential count
- Blood cultures (3x2 bottles)
- Routine blood chemistry, including liver enzymes and bilirubin
- Hepatitis serology (if liver tests abnormal)
- Urinalysis and culture
- Chest radiography



## 1961: Petersdorf and Beeson in Medicine

### Results of 100 patients with FUO



FUO is a huge challenge for physicians and often quite frustrating

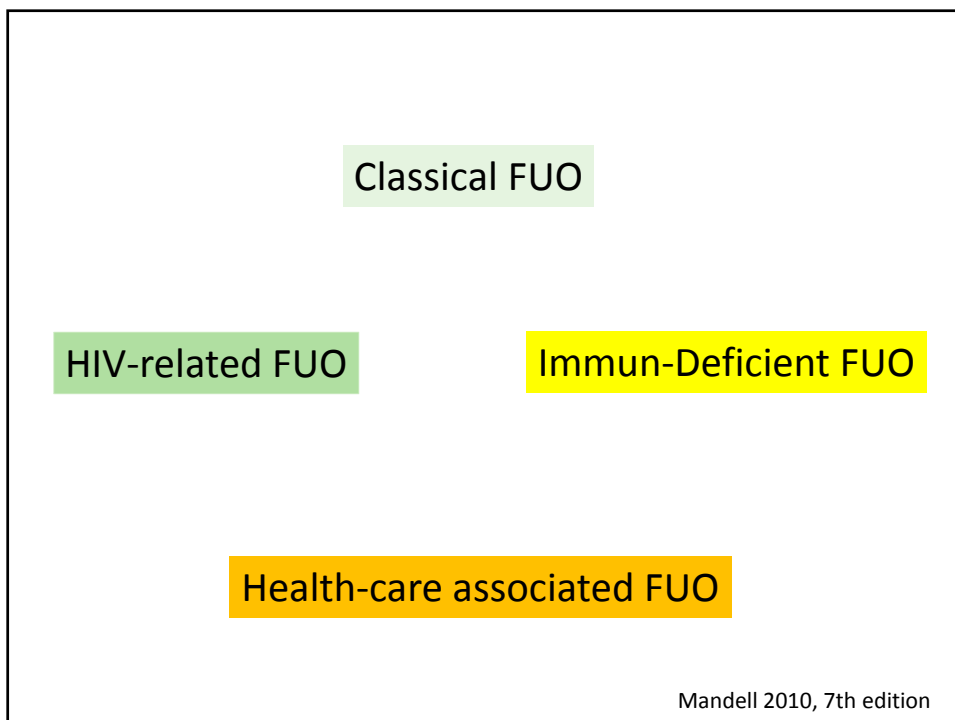
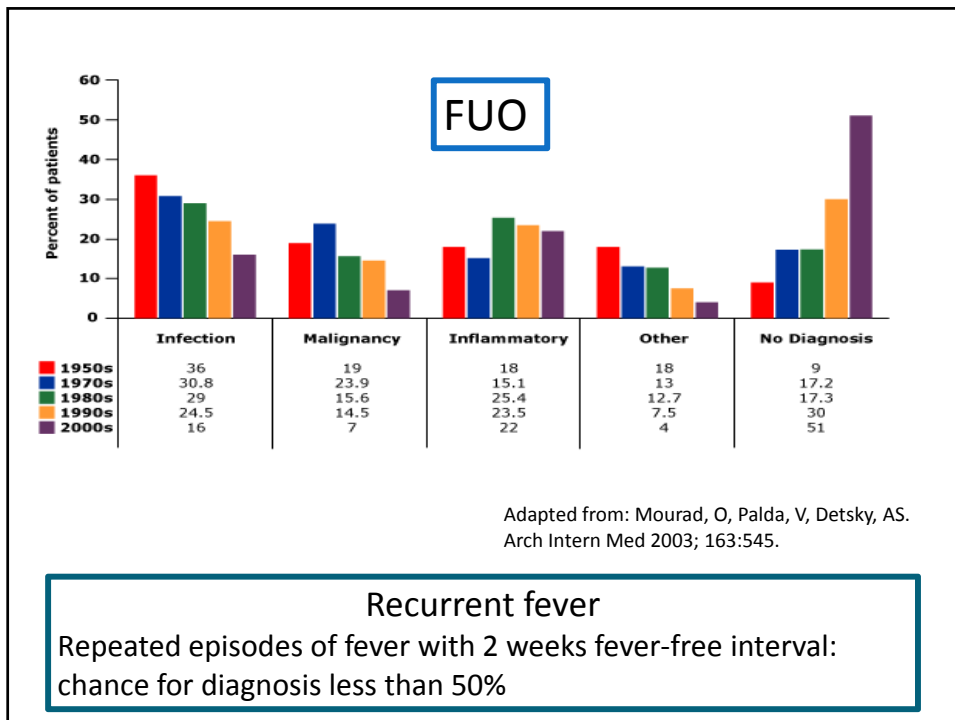
## Definition of FUO

- $> 38.3^{\circ}\text{C}$  on several occasion
- Persisting without diagnosis in spite of 1 week's investigation in hospital

1961 in Medicine, Petersdorf and Beeson

- $> 38.0^{\circ}\text{C}$
- $>3\text{wk}$ ,  $>2$  visits or 3 days in hospital

2010 Mandell, 7th edition



	Classical FVO	Health-care associated FVO	Immune-deficient FVO	HIV-related FVO
Definition	>38°C, > 3 weeks, >3 days in hospitals	>38°C, >3 days, not present ad admission	>38°C, >3 days neg. cultures after 48h	>38°C, > 3 weeks, >3 days in hospitals, HIV
Leading causes	Cancer, infection, inflammatory diseases, undiagnosed	Health-care ass. infections, postoperative complication, drug fever	Mostly infections, not documented in 40-60%	Primoinfection, mycobacteria, CMV, lymphomas, toxoplasmosis, IRIS
Time of investigation	Weeks	Days	Hours	Days to weeks
Time course of disease	Months	Weeks	Days	Weeks to months

## FVO

- The most extensive list of differential diagnosis
- No controlled trials and no meta-analysis
- Prospective multicenter study with a standardized diagnostic protocol 2003-2005

Bleeker-Rovers Ch et al; Medicine 2007

## The most important step...

- Repeated history
- Repeated physical examination
- **Obligatory investigations**

in search for potentially diagnostic clues (PDGs)

## Diagnostic testing may be useful

- Erythrocyte sedimentation rate, CRP
- LDH
- Tuberculin test: Quantiferon
- HIV antibody
- Blood culture over time
- ANCA, Ana, rheumatoid factor
- CMV Ig M antibodies and viral detection in blood
- Serum protein electrophoresis
- Imaging: CT scan of abdomen and chest

Adapted; Arrow PM et al; Lancet 1997

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## **IMAGING**

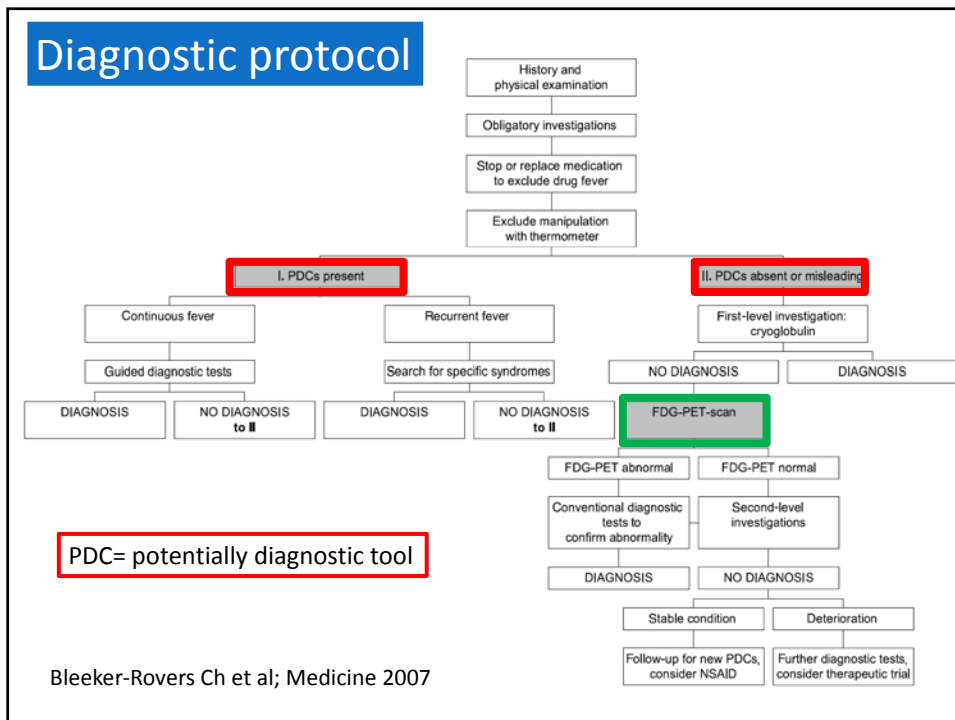
### Imaging

- CT
- MRI
- Ultrasonography

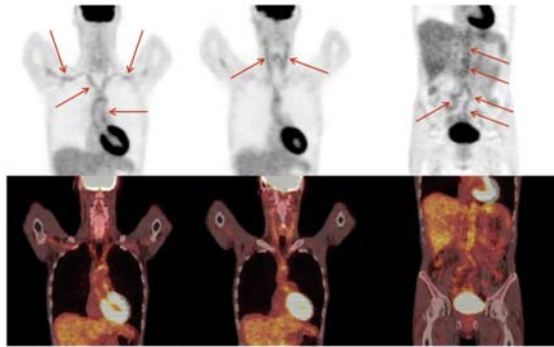
- ❖ Show anatomical changes
- ❖ Foci in an early phase can not be detected
- ❖ Information only of a part of the body

Nuclear imaging techniques permit whole body imaging

Scintigraphic methods			
Chantal P et al; Review, Seminars in nuclear medicine, 2009			
67-Ga-Citrate Scintigraphy	Labeled Leukocyte Scintigraphy	Antigranulocyte Antibodies	FDG-PET (Fluoro-deoxyglucose –Positron emission tomography)
Bind to circulating transferrin, transferred to lactoferrin that is excreted by leukocytes	Ex vivo-labeled autologous leukocytes	Injection of radiolabeled monoclonal antibodies against surface antigens on granulocytes	FDG accumulates in tissue with a high rate of glycolysis
Excreted by kidney Long half-life, high radiation	Accumulation in spleen and liver	Slow diffusion, long half-life, up-take liver	Accumulates in tissue with high glucose consumption, Half-life 110 minutes
High sensitivity, poor specificity (bowel excretion, bone)	Sens. 71-85%, Spec 90-92%	Sens. 40%, Spec 92%	Very high sensitivity, only 1% false positive
Final diagnosis in 99 (68%) of 145 p. with FUO	Helpful in 19 (28%) of 68 patients ; Better for infections than for FUO	34 p. 59% infectious cause of fever, 11% no cause (3)	3 retrospective and 5 prospective studies in 302 p. with FUO Helpful in 36%



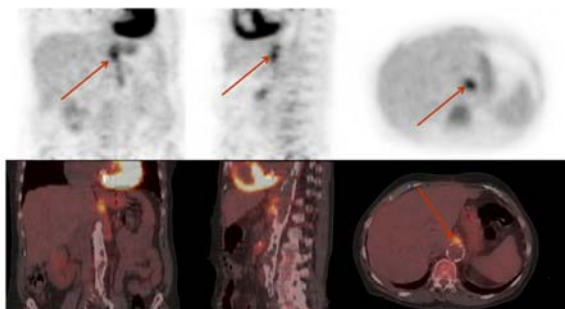
## Vasculitis



**FIGURE 4.** Patient with a history of FOU. Physical examination and ultrasonography of temporal artery were negative. Erythrocyte sedimentation and C-reactive protein were elevated; otherwise, laboratory parameters did not indicate vasculitis.  $^{18}\text{F}$ -FDG PET scan shows increased uptake in thoracic aorta and subclavian arteries (left), carotid arteries (middle), and abdominal aorta together with iliac arteries (right) (arrows). Vasculitis was diagnosed. This example supports role of PET for detection of vasculitis as underlying cause of FOU.

Gotthardt M et al, J Nuc Medicine, 2010

## Vascular graft infection



**FIGURE 2.**  $^{18}\text{F}$ -FDG PET/CT scan of patient with proven *Escherichia coli* infection of vascular graft. Focal, intense uptake of  $^{18}\text{F}$ -FDG (arrows) is sign of infection, in comparison with more diffusely increased physiologic uptake along graft.

Gotthardt M et al, J Nuc Medicine, 2010

## History of a 92-old patient

- February 2011
  - Hosp. with fever, back ache and *Streptococcus constellatus* in blood cultures over 2 days, patient had a pacemaker for over 20 years
  - No focus
  - Hypothesis:
    - Pace-maker-lead infection (echocardiography: no vegetation)
  - Antibiotics
  - After initial improvement
    - CRP increase, fever
  - Ultrasonography of the gallbladder showed stones without signs of inflammation
  - After many weeks: PET-CT:
    - Cholecystitis
    - Operation, since then patient without fever at home



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**BIOPSY**

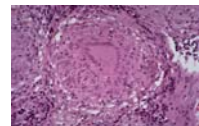
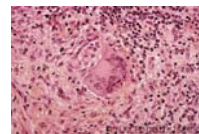
## Liver biopsy: hepatic granulomas

- 66-year woman with weakness, fever over 3 weeks, fatigue
- Blood test: elevated liver enzymes
  - ASAT 202 U/L (<36 U/L) and ALAT 89 U/L (<37 U/L)
  - Bili normal
  - GGT and alkaline phosphatase 2x upper limit of norm

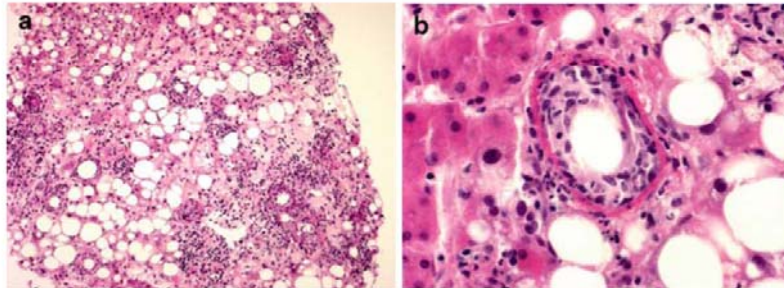
Khanlari B et al, Infection 2008

## Hepatic granulomas

- Noncaseating: sarcoidosis
- Caseating: Tuberculosis
- Lipogranulomas: seen in patients who ingest mineral oil
- Fibrin-ring



## Granulomatous hepatitis with fibrin-ring granulomas



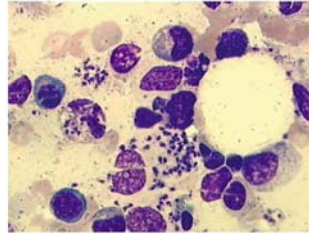
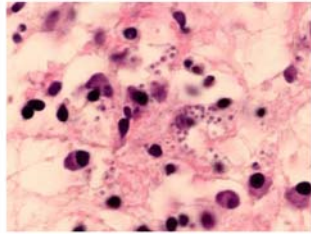
DD: Hodgkin lymphoma, CMV, leishmaniasis, hepatitis A, toxoplasmosis, giant cell arteritis, Rickettsiosis, Q-fever and **use of allopurinol**

## Follow-up...

- Stopp allopurinol
- Fever persisted
- Start with steroids
- Fever decreased
- Patient left the hospital and readmitted 3 weeks later with

**Pancytopenia, elevated liver enzymes**  
– Bone marrow biopsy and liver biopsy

## Visceral Leishmaniasis



Start with liposomal amphotericin B  
Patient developed respiratory problems  
with pneumocystis jirovecii pneumonia  
and died in multiorgan failure

Risk factor: Travel to Malta 2 years ago

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**DRUG FEVER**

## Drug fever

- Fever can be the only features of adverse drug reaction
  - No other signs
  - Eosinophilia or rash can be present but not necessarily
  - Often seen after 3-4 weeks of phenytoin

## Drug-induced Hypersensitivity Syndrome

- Rare event
- Starts 3 weeks to 3 month after starting
  - Carbamazepine, phenytoin, phenobarbital etc.
- Clinic
  - Fever, rash, lymphadenopathy, hepatitis, eosinophilic leukocytosis
- Pathogenesis
  - 1. drug, 2. virus (HHV6 reactivation), 3. interplay with the immune system
- Therapy: Steroids

Shiohara T et al; Clin Rev Allergy Immunol 2007; Gentile et al; BMC Infectious diseases 2010

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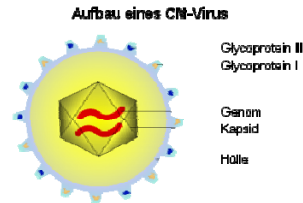
## EXAMPLES

### 64-old female patient

- Fatigue, nausea, fever (37-38.5°C) without chills, coughing, dyspnoea since 4 weeks
- No travel, no pets
- Physical examination: no infectious focus
- Blood smear
  - Lc: 7.3 x10<sup>9</sup>/L with 63% lymphocytes
  - CRP 25 mg/L
  - Liver enzymes 2x upper limit of norm,
- CT lung: normal, no embolisms
- Ultrasonography: liver, spleen, kidney normal
- Gastroscopy: normal, Helicobacter pylori positiv
- Serology for hepatitis A, B, C and E negativ

## Fever, lymphocytosis, liver enzymes?

- CMV primoinfection



Ig G with low avidity (<50%),  
IgM positiv  
positiv PCR with 1000 cp/ml

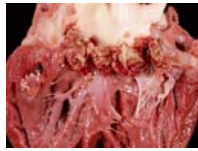
Seroprevalence about 80% at the age of 30

## Diagnostic testing may be useful

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- **CMV Ig M antibodies and viral detection in blood**
- Serum protein electrophoresis
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Adapted; Arrow PM et al; Lancet 1997

## Endocarditis



Native valve endocarditis



Right-side endocarditis  
in drug users

Artificial valve endocarditis



Health-care related endocarditis

## Endocarditis as a cause ofFUO

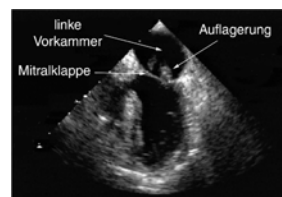
- Blood cultures systems detects easily microorganisms
- Endocarditis less common than some decades ago
- Culture-negative endocarditis:
  - 2.5-31% in the literature

## Endocarditis as a cause of FUO

- Bartonella quintana
- Coxiella burnetii (Q fever) Serology
- Legionella
- Tropheryma whipplesi PCR on valvular tissue

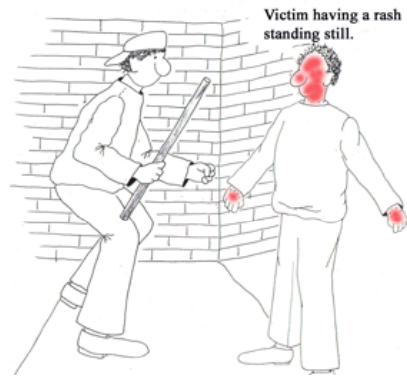
## Personal experience with culture negative endocarditis

- Detected by echocardiography



- Cardiologist calls for further investigation and because of suspected endocarditis

## Adult Still's diseases (juvenile rheumatoid arthritis)



## Adult Still's Disease

- No definite serologic marker
- High spiking fever (40°C)
- Arthralgia or arthritis
- Transient salmon-pink maculopapular rash
- Lymphadenopathy
- Hepatosplenomegaly
- Serositis
- Sore throat



## A long list of possible diagnosis

- Factitious fever
- Thromboembolic disease
- Lymphoma
- Tuberculosis
- etc



Often a well know disease but abnormal presentation

## Management

No therapy until  
the diagnosis is  
made

Often frustrating  
but....

