NUCLEAR MEDICINE IMAGING IN FUO

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NUCLEAR MEDICINE IMAGING IN FUO

- **Definitions and classifications**
- Causes of FUO
- Diagnostic approach

FUO : definition and classification

- **Petersdorf and Beeson 1962**
  - Fever ≥ 38.3 °C on several occasions
  - Illness ≥ 3 weeks duration
  - Diagnosis uncertain after 1 w of in-hospital investigation
- *Medicine 1961; 40: 1-30*

- **Durack and Street 1991**
  - Classical FUO
    - Fever ≥ 38.3 °C on several occasions
    - Illness ≥ 3 weeks duration
    - Diagnosis uncertain after 3 d of in-hospital investigation or 3 out-patient visits
  - Nosocomial FUO
  - Neutropenic FUO
  - HIV-associated FUO
- *Curr Clin Top Inf Dis 1991; 11: 35-51*

TABLE 1
Classification of Fever of Unknown Origin (FUO)

Category of FUO	*Definition*	*Common etiologies*
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 mm^3 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

HIV = human immunodeficiency virus.

Adapted with permission from Durack DT, Street AC. Fever of unknown origin—reexamined and redefined. Curr Clin Top Infect Dis 1991;11:37.

Roth et al. Am Fam Physician: 2003; 68:2223-2238

FUO : future definition

- Illness > 3 weeks duration
- Temperature ≥ 38.3 °C or lower with laboratory signs of inflammation on ≥ 3 occasions
- Lack of diagnosis or reasonable hypothesis after a relevant diagnostic investigation
- Exclusion of nosocomial fevers and severe immunocompromise

- *Bleeker-Rovers et al. FUO. Sem Nucl Med 2009; 39: 81-87*

FUO : DEFINITION

Table 1. Minimal Diagnostic Workup to Qualify as Fever of Unknown Origin

Comprehensive history
Physical examination
Complete blood cell count + differential
Blood film reviewed by hematopathologist
Routine blood chemistry (including lactic dehydrogenase, bilirubin, and liver enzymes)
Urinalysis and microscopy
Blood (×3) and urine cultures
Antinuclear antibodies, rheumatoid factor
Human immunodeficiency virus antibody
Cytomegalovirus IgM antibodies; heterophil antibody test (if consistent with mononucleosis-like syndrome)
Q-fever serology (if exposure risk factors exist)
Chest radiography
Hepatitis serology (if abnormal liver enzyme test result)

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TABLE 2
Common Etiologies of Fever of Unknown Origin

Infections	Autoimmune conditions
Tuberculosis (especially extrapulmonary)	Adult Still's disease
Abdominal abscesses	Polymyalgia rheumatica
Pelvic abscesses	Temporal arteritis
Dental abscesses	Rheumatoid arthritis
Endocarditis	Rheumatoid fever
Osteomyelitis	Inflammatory bowel disease
Sinusitis	Reiter's syndrome
Cytomegalovirus	Systemic lupus erythematosus
Epstein-Barr virus	Vasculitides
Human immunodeficiency virus	**Miscellaneous**
Lyme disease	Drug-induced fever
Prostatitis	Complications from cirrhosis
Sinusitis	Factitious fever
Malignancies	Hepatitis (alcoholic, granulomatous, or lupoid)
Chronic leukemia	Deep venous thrombosis
Lymphoma	Sarcoidosis
Metastatic cancers	Habitual Hyperthermia
Renal cell carcinoma	
Colon carcinoma	
Hepatoma	
Myelodysplastic syndromes	
Pancreatic carcinoma	
Sarcomas	

Big Three

MinorThree

TABLE 3
Agents Commonly Associated with Drug-Induced Fever

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

Roth et al. Am Fam Physician: 2003; 68:2223-2238

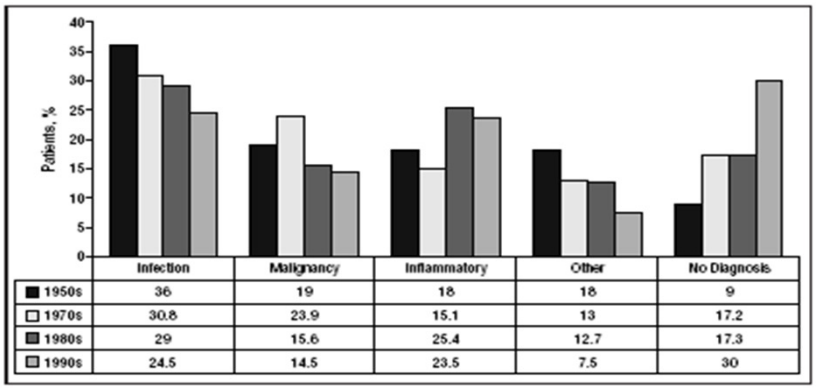
CAUSES OF FUO: MOST FREQUENT

- **Endocarditis, TB, abdominal abcesses, EBV and CMV**
- **Lymphoma, leukemia**
- **Adult onset Still disease, SLE, PMR/giant cell arteritis, sarcoidosis**
- **M. Crohn, subacute thyroiditis, habitual hyperthermia (young woman, neurotic, months to years, low grade, fatigue, myalgia, ..), drug fever**

CAUSES OF FUO: Spectrum def. factors

- Time era of the study (diagnostic means)
- Geographic factors
- Patient age
- Duration of the fever
- Type of hospital

CAUSES OF FUO: ERA-RELATED



	Infection	Malignancy	Inflammatory	Other	No Diagnosis
1950s	36	19	18	18	9
1970s	30.8	23.9	15.1	13	17.2
1980s	29	15.6	25.4	12.7	17.3
1990s	24.5	14.5	23.5	7.5	30

Figure 1. The percentage of patients with fever of unknown origin by cause over the past 40 years.

Mourad et al. Arch Int Med 2003; 163: 545

Influence of age (FUO)

	Elderly(n=204)	Young(n=152)
Infection	72(35)	33(21)
-Tuberculosis	20(10)	4(3)
-Abscess	25(12)	6(4)
-Endocarditis	14(7)	2(1)
-Viral	1(0.05)	8(5)
Tumour	38(19)	8(5)
SID's	57(28)	27(17)

Norman D., Clin Inf Dis 2000; 31: 148

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Diagnostic approach of FUO

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  - Total body inflammation/inefction scan
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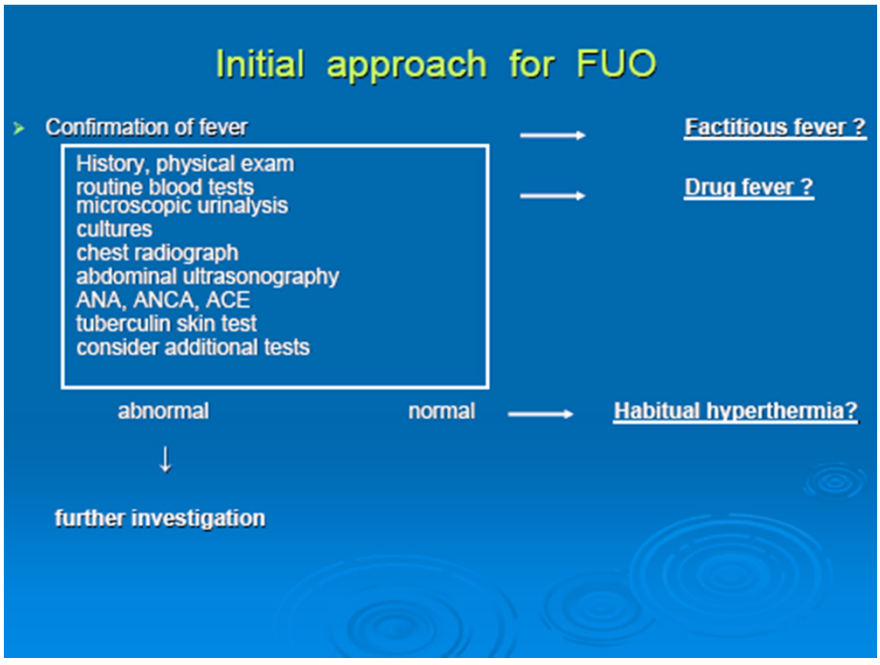
  - Wait and see strategy



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Total Body Inflammation/infection scan

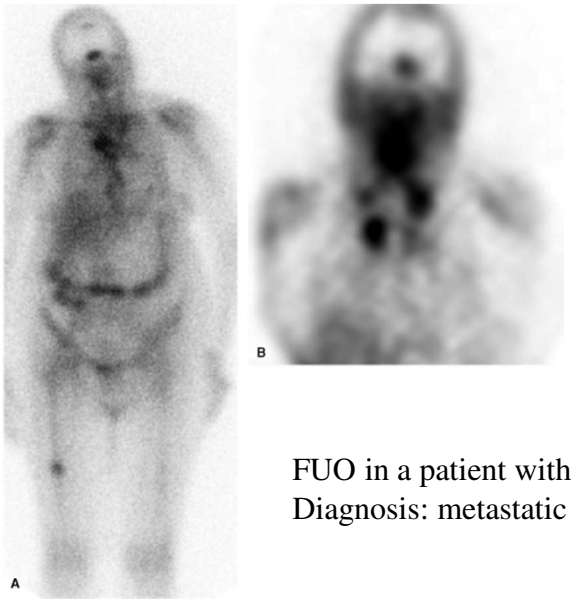
- ^{67}Ga-scintigraphy
- Labeled leucocytes
- FDG PET

67Ga-scintigraphy in FUO

Long time assumed « gold standard »,

- Pros'
  - acute and chronic inflammatory conditions
  - Some neoplasms
- Con's
  - Poor specificity
  - Duration of imaging, suboptimal decay

- Largest study: Knockaert et al. Clin Infect Dis 1994;18
  - N=145 pts (1980-1989)
  - Final diagnosis available in 68% (99pts)
  - 82 abnormal scans (57%), 42 of these were helpfull (49%)



FUO in a patient with a history of RCC
Diagnosis: metastatic disease

Total Body Inflammation/infection scan

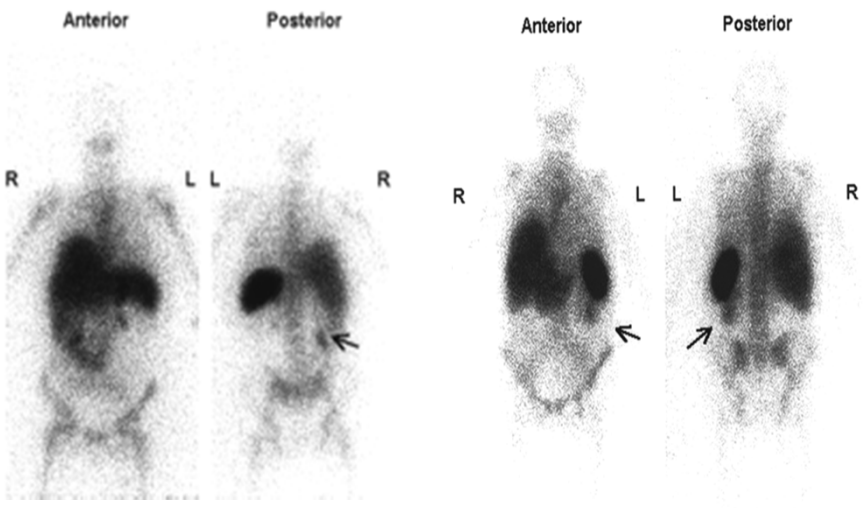
- ^{67}Ga-scintigraphy
- Labeled leucocytes
- FDG PET

^{111}In-oxine WBC in FUO

	Nb	Se	Spe.	Accuracy
• Syrjala et al.1987(JNM)	68	81%	90%	87%
• Schmidt et al. 1987(SJID)	32	?	100%	?
• McSweeneyet al. 1990(ClRad)	25	55%	79%	74%
• Kjaer et al. 2002(JNM)	31	75%	83%	-

^{99m}TC-antigranulocyte Ab scintigraphy

•Becker et al. 1993(EJNM)	34	40%	90%
•Meller et al. 1998(JNM)	51	helpfull in 27% of pts.	



Kjaer et al. JNM; 2002

Total Body Inflammation/infection scan

- ^{67}Ga-scintigraphy
- Labeled leucocytes
- FDG PET
  - Summary
  - Examples

FDG PET(-CT) IMAGING IN FUO

TABLE I.—*Studies with FDG-PET in patients with classical FUO.*

Author	Design	Patients (n=292)						PET helpful (%)
		N.	IF (%)	ID (%)	NP (%)	MISC (%)	ND (%)	
Meller *et al.*[52]	p	20	40	25 (15)	10	15	10	55 (PPV: 92; NPV: 75)
Blockmans *et al.*[54]	p	58	18	29 (14)	10	9	34	41 (PPV: —; NPV: —)
Lorenzen *et al.*[53]	r	16	19	50 (18)	6	6	19	69 (PPV: 92; NPV: 100)
Bleeker-Rovers *et al.*[55]	r	35	17	11 (3)	17	9	46	37 (PPV: 87; NPV: 95)
Kjaer *et al.*[56]	p	19	26	16 (5)	6	16	36	16 (PPV: 30; NPV: 67)
Buysschaert *et al.*[57]	r	74	9	5 (4)	16	19	51	26 (PPV: —; NPV: —)
Bleeker-Rovers *et al.*[58]	p	70	17	23 (4)	7	3	50	33 (PPV: 70; NPV: 92)

FDG: 2-[^{18}F]fluoro-2-deoxy-D-glucose; PET: positron emission tomography; FUO: fever of unknown origin; n.: percentage of patients with medium- and large sized vasculitis in a study; IF: infection; ID: inflammatory non-infectious disease; NP: neoplasia; MISC: miscellaneous disorders; ND: non-diagnostic scans; p: prospective, r: retrospective; PPV: positive prospective value; NPV: negative prospective value.

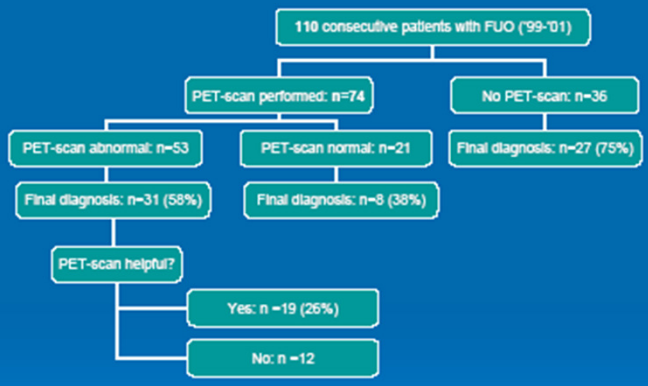
(Cum: 104/292 = 36%)

Meller et. al, Q J Nucl Med Mol Imaging 2009; 53:51

Difficult comparison between studies

- Definition of FUO differs
- Patient recruitment: classic FUO or postoperative sepsis
- FDG-PET technique
- No standardized diagnostic protocol
- No final diagnosis in all patients

Retrospective study of FDG-Pet in FUO (n=74)



FDG-PET was helpful in **26%** (19/74) of the patients with FUO
FDG-PET was helpful in **49%** (19/39) of the patients with final diagnosis

Europ J Int Med 2004; 15: 151-6

Table 3
Predictors of helpful FDG-PET

Variable	FDG-PET helpful (*N*–19)	FDG-PET noncontributory (*N*–55)	*P*
Male gender	10 (53)	30 (55)	0.9
Age, years	57 (38–73)	50 (30–66)	0.1
Episodic fever	5 (26)	25 (46)	0.1
Duration of illness, days	30 (21–140)	60 (22–120)	1.0
Maximum temperature, °C	39.0 (38.5–39.5)	39.2 (38.8–40.0)	0.2
Erythrocyte sedimentation rate, mm/h	78 (56–110)	52 (25–103)	0.1
C-reactive protein, mg/l	67 (19–120)	77 (38–158)	0.6
Hemoglobin, g/l	11.6 (10.0–12.0)	11.6 (10.4–13.5)	0.6

Data represent number (percentage) or median (interquartile range).

Diagnostic contribution of Gallium-67-scintigraphy and PET-scintigraphy in 40 patients with FUO who underwent both examinations

	PET scan			Galliumscan		
Diagnostic category	normal	contributory	non-contributory	normal	contributory	non-contributory
infections (n = 8)	0	4	4	3	3	2
tumours (n = 3)	1	1	1	1	0	2
multi-system diseases (n = 12)	2	8	2	3	6	3
(vasculitis n = 4)	(0)	(4)	(0)	(2)	(2)	(0)
miscellaneous (n = 3)	2	1	0	1	1	1
no diagnosis (n = 14)	4	0	10	5	0	9
total (n = 40)	9	14 (35 %)	17	13	10 (25 %)	17

Blockmans et al. Clin Infect Dis 2001; 32

FDG-PET compared to Gallium:

- FDG-PET scan is at least as good as Gallium-scintigraphy: every pathology detected with Gallium-scintigraphy was also revealed by FDG-PET
- Major advantage of FDG-PET : the vascular uptake of FDG in patients with large vessel vasculitis (giant cell or temporal arteritis (Horton disease), polymyalgia rheumatica and Takayasu arteritis)
- Shorter duration of investigation (2h vs 72h)
- Higher spatial resolution
- Better evaluation of the abdomen

FDG PET(-CT) IMAGING IN FUO

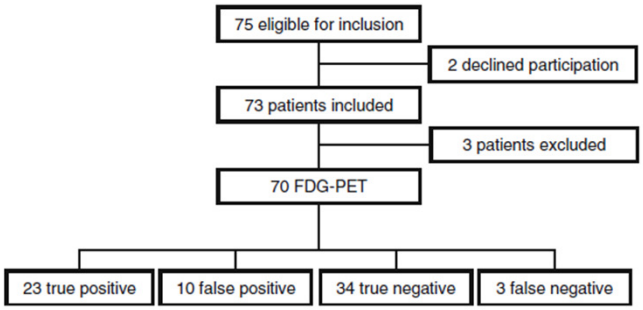


Fig. 2 Three patients had to be excluded: all symptoms resolved before FDG-PET was performed in one patient; in another patient, it proved impossible to obtain a reliable FDG-PET scan owing to severe contractures of the extremities; and one patient died before FDG-PET was performed

Bleeker-Rovers, EJNMI 2007; 34:694-703

FDG PET(-CT) IMAGING IN FUO

- 70% of abnormal FDG-PET scans were clinically helpful
- FDG-PET contributed to the ultimate diagnosis in 33% of all patients
- FDG-PET contributed significantly more often to the final diagnosis in patients with continuous fever vs periodic fever (45% vs 12%, p<0.005)
- FDG-PET did not contribute in patients with normal CRP
- False positive PET results were responsible for less than 1 % of all diagnostic studies performed in these pts

Bleeker-Rovers, EJNMI 2007; 34:694-703

FDG PET(-CT) IMAGING IN FUO

- Advantages of FDG-PET
  - High resolution
  - Sensitivity in chronic low-grade infections
  - High accuracy in the central skeleton
  - Detection of vasculitis
- Theoretical disadvantage impossibility of differentiating between malignancy and infectious diseases or inflammation
- Disadvantages of FDG-PET
  - Relatively high cost
  - Limited availability

- Conclusion:
- FDG-PET is a valuable imaging technique as part of a structured diagnostic protocol in patients with FUO and raised CRP
- Very high negative predictive value

Bleeker-Rovers, EJNMI 2007; 34:694-703

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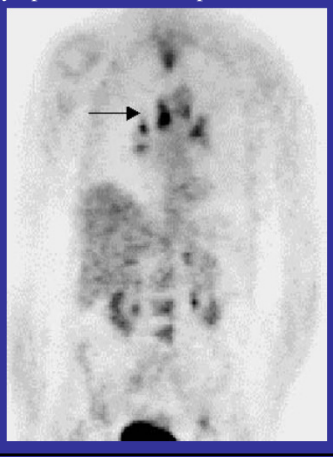
FDG PET(-CT) IMAGING IN FUO

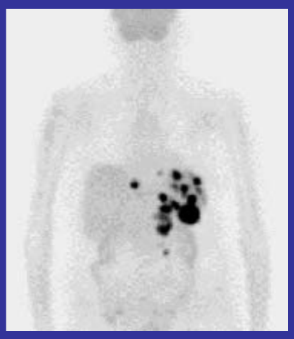
- 70-year-old female
- fever, fatigue and weight loss of 3 weeks' duration.
- A lymph node biopsy obtained by mediastinoscopy demonstrated granulomatous inflammation confirming a diagnosis of sarcoidosis.
- Symptoms resolved upon treatment with corticosteroids



Bleeker-Rovers, EJNMI 2007; 34:694-703

FDG PET(-CT) IMAGING IN FUO

- 76-year-old female
- Fever and weight loss
- Blood,urine, broncho-alveolar lavage fluid and bone marrow cultures
- were negative.
- Chest X-ray, abdominal and thoracic CT scans, MRI of the spine, bone scan, lung perfusion scintigraphy, 111In-WBC scan, gastroscopy, colonoscopy and bronchoscopy were all normal.
- Duodenum, liver, bone and temporal artery biopsies were normal.



Bleeker-Rovers, EJNMI 2007; 34:694-703

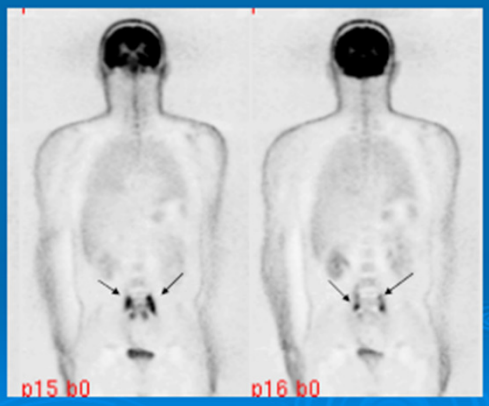
Infected vascular prosthesis

A 49-year-old man with episodic fever (38,5°C) since one year with night sweats, weight loss and a vague discomfort in the hips.

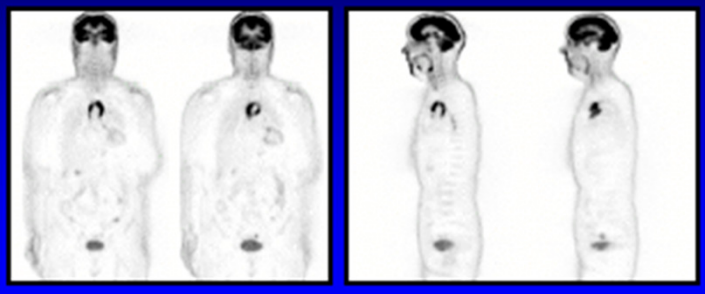
ESR was 93 mm/h (normal <10 mm/h) and CRP 69 mg/L (normal <5 mg/L).

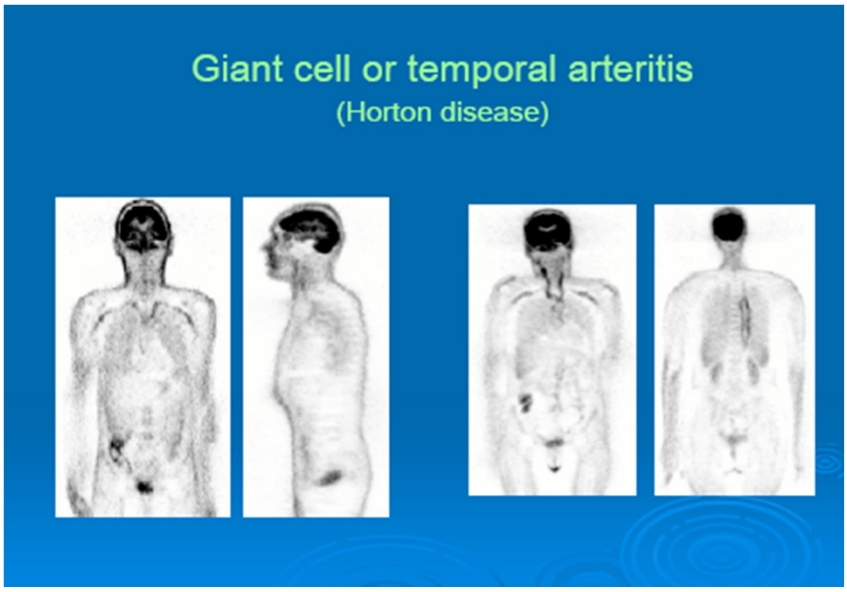
^{18}FDG-PET scan shows increased uptake in the lumbar spine around orthopaedic prosthesis material *(arrows)*.

Culture of the removed material revealed growth of Staphylococcus warneri, successfully treated with antibiotics.



Aortitis





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Therapeutic trials

- NSAID, cave Still's disease (hepatotoxicity
- If clinical deterioration (only than)
  - AB's
    - Broad spectrum (re-assessment after 3-4 days, if no response, stop)
    - Tetracyclines?
  - Anti-TB
  - Corticosteroids (never without anti-TB), late

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FUO in surviving undiagnosed cases (n=49)

- Spontaneous resolution (during/shortly post-hosp) n=31
- Persisting or recurring fever (>3 m post-discharge) n=18
  - Cured : n=10
  - Unresolved : n= 8
    - Treated with corticosteroids n= 1
    - Treated with NSAID n=6
    - Refused reinvestigation and died n=1

Knockaert et al. Arch Int Med 1996; 156: 618

Thank you for your attention