

The diagnostic approach of FUO

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FUO: traditional definition

Petersdorf and Beeson '61⁽¹⁾

1. Fever $\geq 38,3^{\circ}\text{C}$ on several occasions
2. Illness ≥ 3 weeks' duration
3. Diagnosis uncertain after 1 week of in-hospital investigation

Durack and Street '91⁽²⁾

Classical FUO

1. Fever $\geq 38,3^{\circ}\text{C}$ on several occasions
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3. Diagnosis uncertain after 3 d of in-hospital investigation or 3 out-patient visits

(Nosocomial FUO)

(Neutropenic FUO)

(HIV-associated FUO)

⁽¹⁾*Medicine '61;40:1-30*

⁽²⁾*Curr Clin Top Inf Dis '91;11:35-51*

Habitual hyperthermia

“Psychogenic fever”

- young women
- neurotic traits
- low grade fever 38 - 38.5° C
- months to years
- influence of physical and intellectual activity
- fatigue
- myalgia

Reimann JAMA 1932, 99, 1860.

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FUO: a definition for the next decades

- Illness of more than 3 weeks' duration
- Temperature of at least 38.3°C or lower temperature with laboratory signs of inflammation on at least 3 occasions
- No diagnosis or reasonable (eventually confirmed) diagnostic hypothesis after an initial intelligent (in- or outpatient) diagnostic investigation*
- Exclusion of nosocomial fevers and severe immunocompromise.

Minimum diagnostic evaluation to qualify as fever of unknown

- **Comprehensive history** (including accompanying symptoms, travel history, sexual risk behaviour, profession, hobbies, contact with animals [pets, birds, insects] and ill persons, family history, use of medications and illicit drugs, past medical and surgical history, presence of foreign material)
- **Meticulous physical examination** (eyes, mucosal surfaces, temporal arteries, skin, hands and nails, lymph nodes, thyroid, heart, lungs, abdomen, rectal examination, musculoskeletal system, neurological examination, vascular examination)
- **Routine blood tests:** ESR, CRP, protein electrophoresis, WBC count including differential and platelet count, blood chemistry, including creatinin, sodium, potassium, enzymes (lactate dehydrogenase, bilirubin, liver enzymes, and creatine phosphokinase)
- **Urinalysis**, including microscopic examination
- **Immunological tests:** ANF, ANCA, ACE
- **Cultures:** Routine blood and urine cultures while not receiving antibiotics, cultures of other otherwise sterile fluids (e.g., from joints, pleura, or cerebrospinal space) whenever appropriate
- **Tuberculin skin test**
- **Chest X-ray**
- **Abdominal ultrasonography** (incl. pelvis)
- **Further evaluation of any abnormalities detected by above tests** (e.g., HIV testing in case of suspicious exposure, echocardiography in case of cardiac murmur, blood smear for malaria in the traveller, cytomegalovirus serology in case of reactive lymphocytosis, ...)

CAUSES of FUO

- infections*
 - tumours
 - systemic inflammatory diseases
rheumatological disorders, connective tissue diseases,
vasculitides, sarcoidosis
 - miscellaneous
 - drug fever
 - factitious fever
 - habitual hyperthermia
 - others
- big three*
- minor three*

- *
 - not diagnosed
 - not effectively treated: endocarditis, osteomyelitis, abscess
 - slowly responding to treatment (e.g. tb, endocarditis)

Infectious causes of FUO

- Tuberculosis
- localized bacterial infections
 - endocarditis, abscess, dental and sinus infections, urinary tract infections (prostate, ...), osteomyelitis,...
- systemic bacterial infections
 - (e.g. typhoid fever, brucellosis, Borrelia, syphilis, Whipple disease,.....)
- Rickettsial diseases (Coxiella, Bartonella, Ehrlichia)
- viral diseases (CMV, EBV, HIV, Parvo B19, hepatitis)
- Chlamydia, mycoplasma
- parasitic diseases: universal parasites
"tropical" parasites
- fungal diseases

Neoplastic causes of FUO

- haematological:
 - diffuse : (aleukemic) leukemia
myelodysplasia
 - focal : lymphoma, myeloma
- solid tumours
- atrial myxoma

SID's as cause of FUO

- multisystem diseases
- rheumatological disorders
- connective tissue diseases
- vasculitides
- granulomatous diseases: sarcoidosis


Miscellaneous Causes of FUO

- deep venous thrombosis - pulmonary embolism
- hematoma (including dissecting aneurism)
- Crohn's disease
- non-malignant lymphoproliferative disorders (Castleman's disease, Kikuchi's disease, inflammatory pseudotumor of lymph nodes, angio-immunoblastic lymphadenopathy)
- Familial Mediterranean Fever
- hypersensitivity pneumonitis
- hyper IgD syndrome
- endocrine disorders (thyroiditis,.....)
-

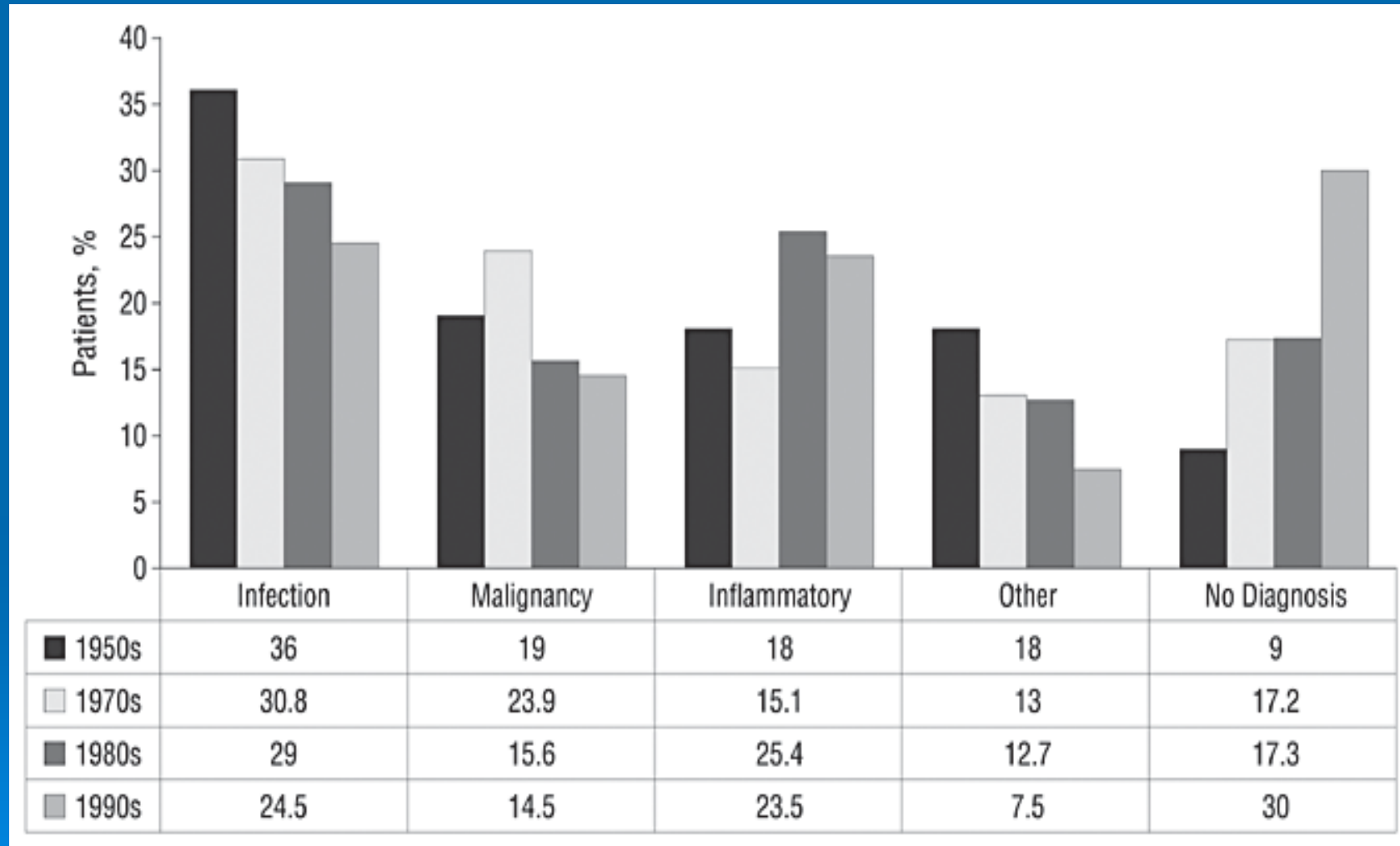
Most common of the more than 200 different causes of FUO

- Endocarditis, tuberculosis, abdominal abscess
Epstein-Barr and cytomegalovirus infection
- Lymphoma, (aleukemic) leukemia
- Adult-onset Still disease, systemic lupus erythematosus, giant cell arteritis/polymyalgia rheumatica, sarcoidosis
- Crohn's disease, subacute (De Quervain) thyroiditis
habitual hyperthermia, drug fever

Spectrum of causes of FUO

- Influenced by - the time of the study (diagnostic means)
- geographic factors
 - age of the patients
 - duration of fever
 - type of hospital
- 

Causes of FUO



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

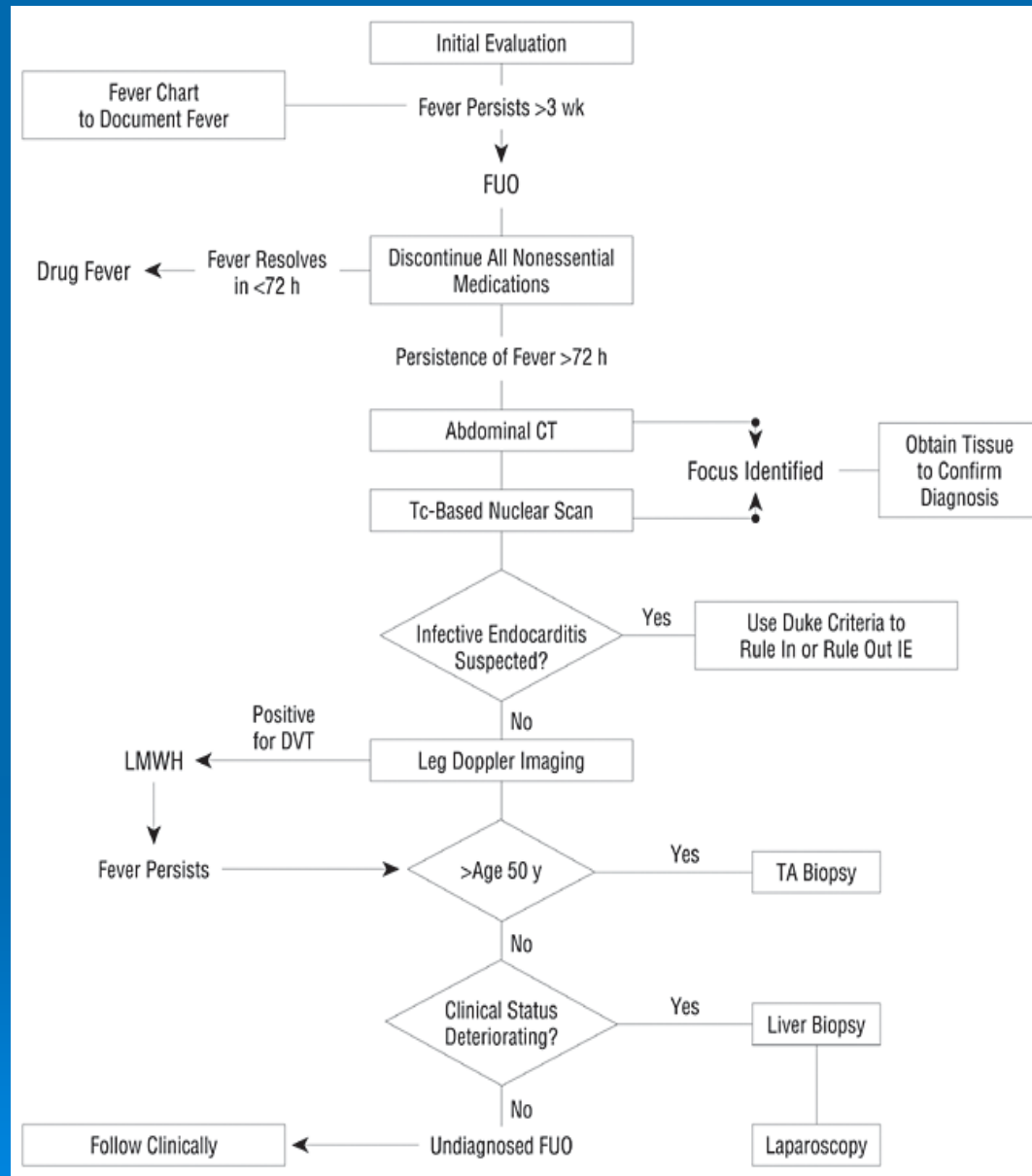
Influence of age on the disease spectrum of FUO

	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 (.05)	8 (5)
Tumour	38 (19)	8 (5)
SID'S	57 (28)	27 (17)

Diagnostic approach of FUO

- **look for potentially diagnostic clues**
“directed” investigation
- **if no clues or negative directed investigation:**
 - ***staged approach (algorithm)***
 - total body inflammation scintigraphy
 - therapeutic trials
 - wait and see strategy

Proposed algorithm for an approach to FUO.



Mourad et al. Arch Int Med
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Initial approach for FUO

➤ Confirmation of fever

History, physical exam
routine blood tests
microscopic urinalysis
cultures
chest radiograph
abdominal ultrasonography
ANA, ANCA, ACE
tuberculin skin test
consider additional tests

abnormal

normal

→ Factitious fever ?

→ Drug fever ?

→ Habitual hyperthermia?



further investigation

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- **look for potentially diagnostic clues**
“directed” investigation
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Which radionuclide technique for FUO ?

- Labeled leukocytes (Indium, technetium.....)
- Labeled immunoglobulins (Indium, technetium.....)
- Gallium citrate
- Labeled monoclonal antiggranulocyte antibodies (anti NCA-95, anti NCA-90,...)
- Labeled antibiotics (TC-99m ciprofloxacin)
- FDG-PET
-

“Infection and inflammation” radiopharmaceuticals



Role of nuclear medicine in FUO

- total body assessment
- “guidance”: *localize the source of fever* and guiding additional diagnostic procedures (eg US-, CT- or MRI-guided biopsy, endoscopy, surgical biopsy,.....)

Interpretation of nuclear medicine studies in FUO

➤ Positive (abnormal accumulation)

- helpful to diagnosis
- non-contributory to diagnosis (either false positive or unexplained because of lack of final diagnosis or limited investigation of the abnormal focus)

➤ Negative (normal distribution of the tracer)

- true negative
- false negative in case of FDG-PET due to tumour size, type of tumour (low grade well differentiated tumours such as (some) prostate and thyroid cancers)

The concepts of Se, Sp, PPV, NPV can not be applied because many cases remain undiagnosed and several diseases that cause FUO do not give rise to abnormal tracer accumulation.

FDG-PET

¹⁸fluoro-2-deoxy glucose positron emission tomography

FDG is a glucose analogue, marked with Fluor-18, which is taken up in cells, phosphorylated but not further metabolized (“trapped in the cell”)

The cellular uptake is related to metabolic rate; fastly dividing (neoplastic) or “active” (inflammation) cells need more “fuel”, take up more glucose

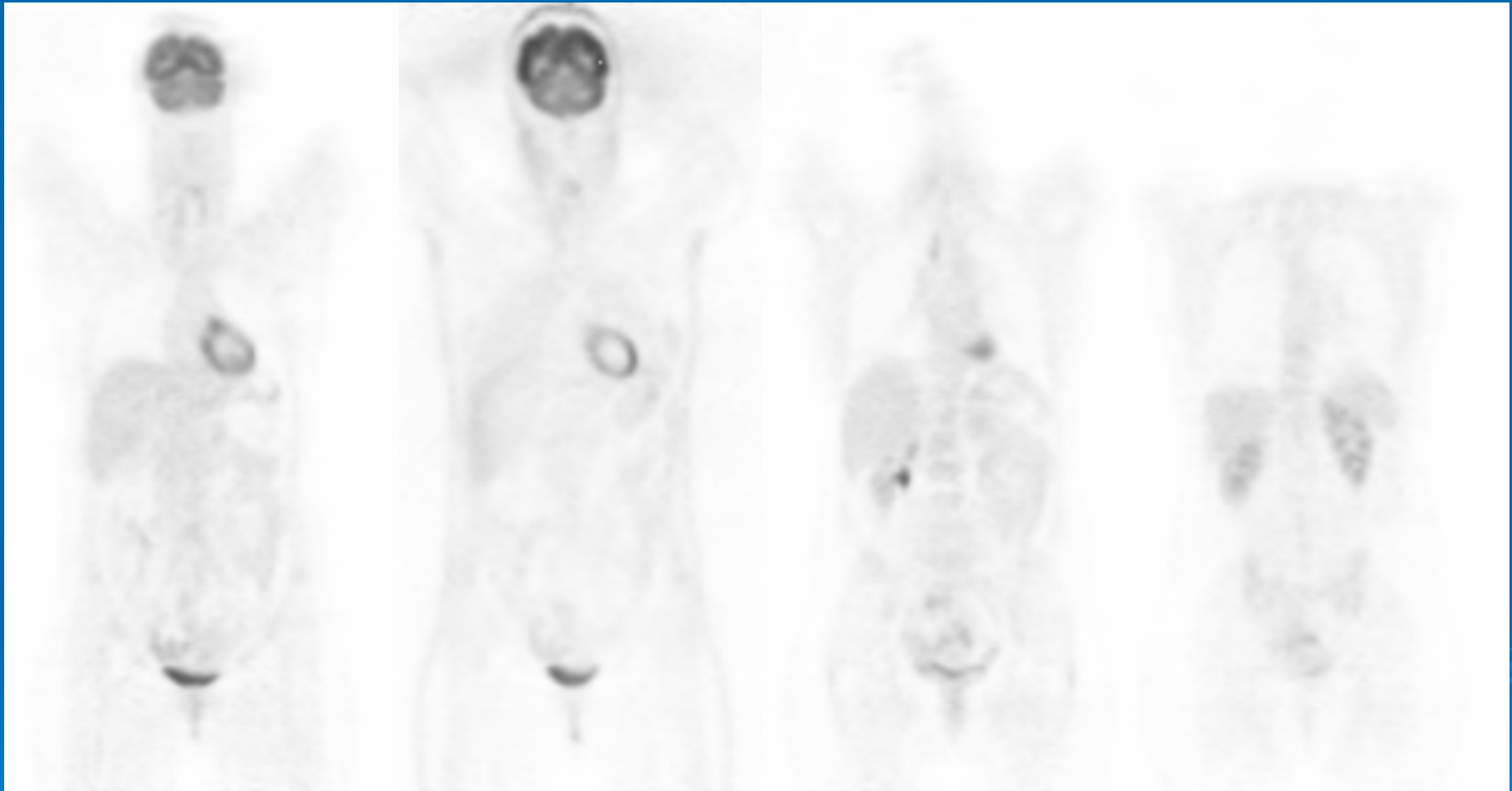
increased FDG uptake is not tumour specific!!!

FDG uptake is also increased in active infections, abscesses, tb, healing wounds, hematomas, inflammation sites (sarcoidosis, vasculitis,),...

FDG is excreted in the urine

Brain, heart and urinary tract rather difficult to assess because of high background uptake

Normal FDG-PET images



FDG-PET

- Radiative burden: 10-15 mCi (370-550 MBq)
- Less than 0,5 microgr of FDG per study
- Short half-life (110 min)
- Patients have to fast to reduce competition for glucose transporters
- Indications for use
 - staging of tumours and response to treatment
 - assessment of myocardial viability
 - neuro-imaging (epilepsy,.....)
 - whole body inflammation tracer
- Approved in USA in 1998

Pilot study of FDG-PET in 58 cases with classical FUO (1996-98)

➤ *final diagnosis* in 40 patients (69 %)

- infections : 12 (30 %)
- tumours : 6 (15 %)
- SID's (vasculitis n = 8) : 17 (43 %)
- miscellaneous : 5 (12 %)

➤ *no diagnosis* in 18 patients (31 %)

Results: FDG – PET in FUO (n=58)

- 12/58 normal (21 %)
- 46/58 abnormal (79 %)

24 contributory (helpful) to diagnosis (41 %)

22 non-contributory (38 %)

Pilot study of the diagnostic contribution of **FDG-PET-scintigraphy** in FOU (n=58) (1996-1998)

Diagnostic category	normal	contributory	non-contributory
infections (n = 12)	2	6	4
tumours (n = 6)	2	3	1
multi-system diseases (n=17)	2	12	3
(vasculitis n = 8)	(0)	(7)	(1)
miscellaneous (n = 5)	2	3	0
no diagnosis (n = 18)	4	0	14
total (n = 58)	12	24	22
	(21%)	(41 %)	(38%)

Neurotuberculosis



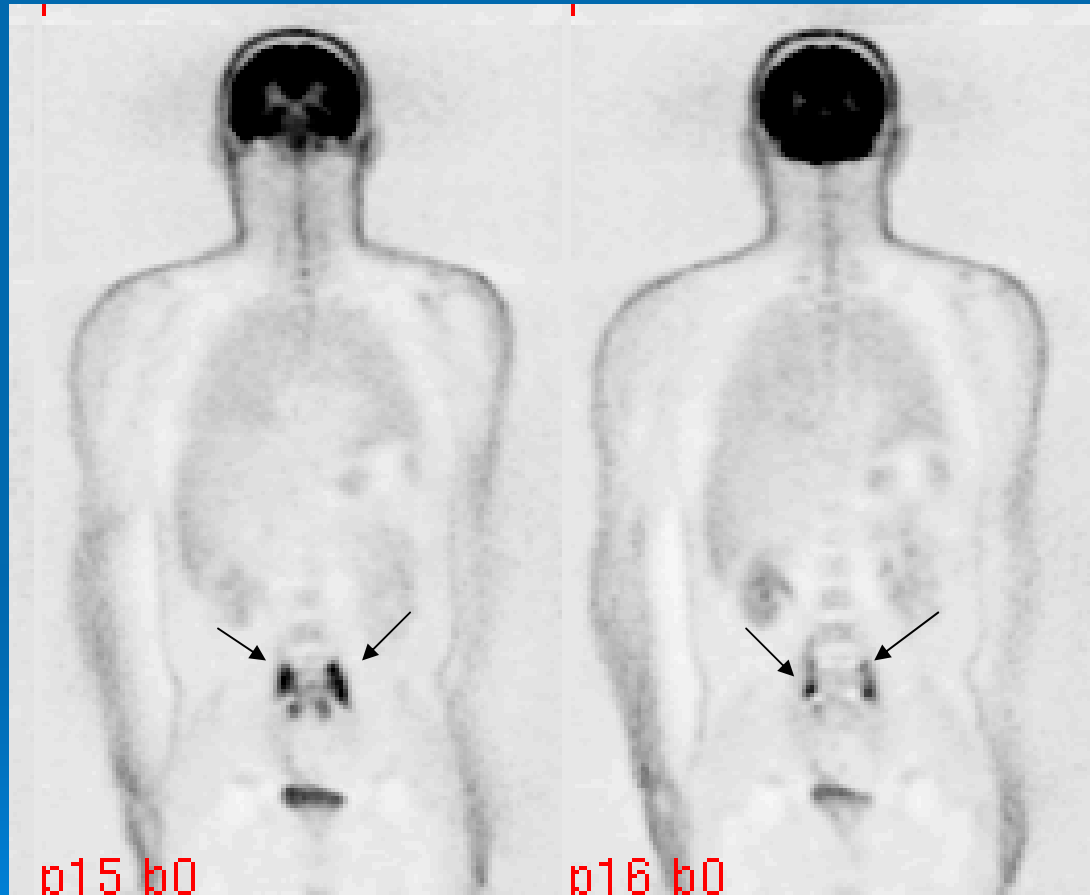
Infected vascular prosthesis

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.

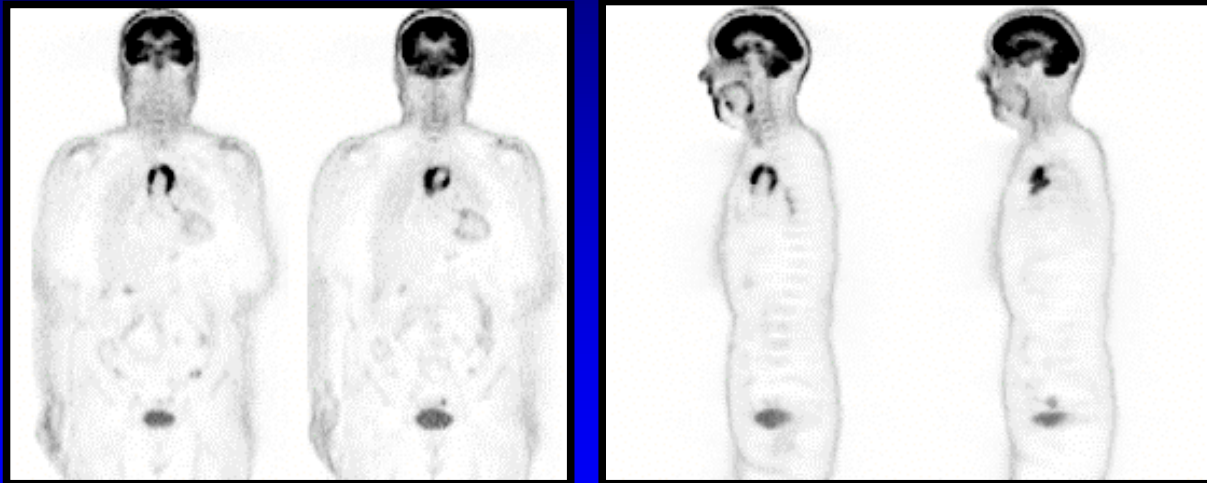
ESR was 93 mm/h (normal <10 mm/h) and CRP 69 mg/L (normal <5 mg/L).

¹⁸F-DG-PET scan shows increased uptake in the lumbar spine around orthopaedic prosthesis material (*arrows*).

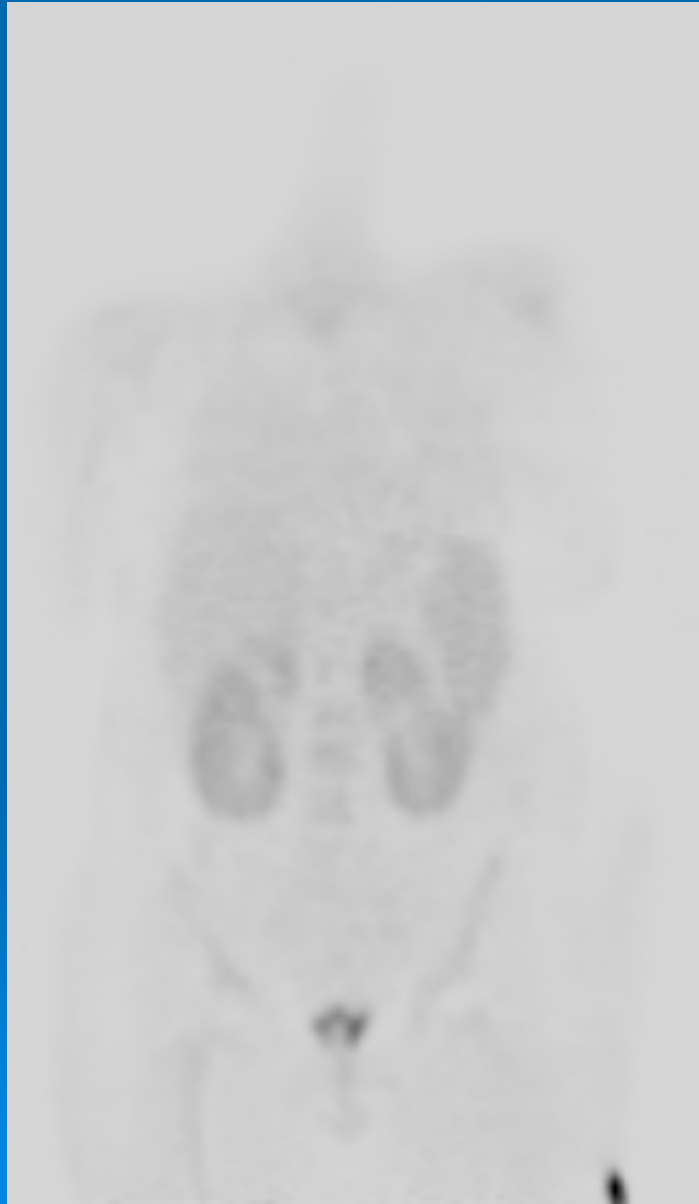
Culture of the removed material revealed growth of *Staphylococcus warneri*, successfully treated with antibiotics.



Aortitis



Intravascular Lymphoma



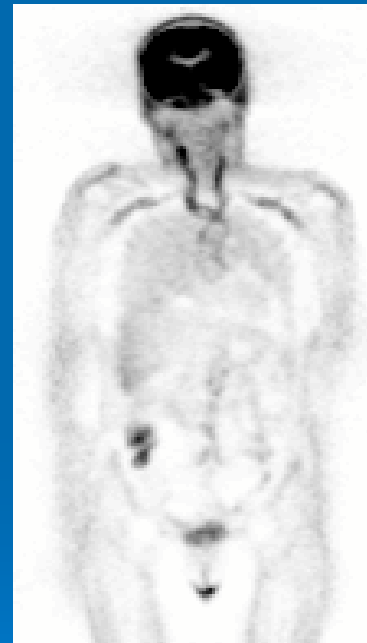
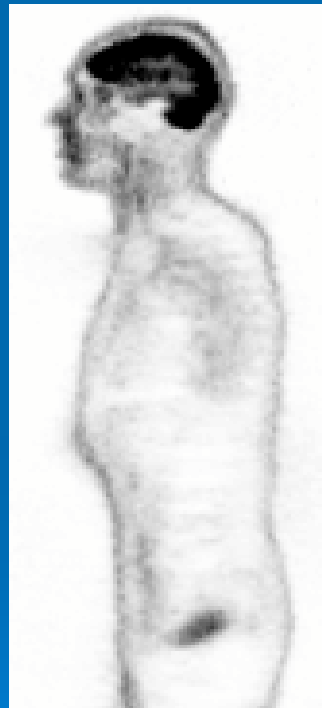
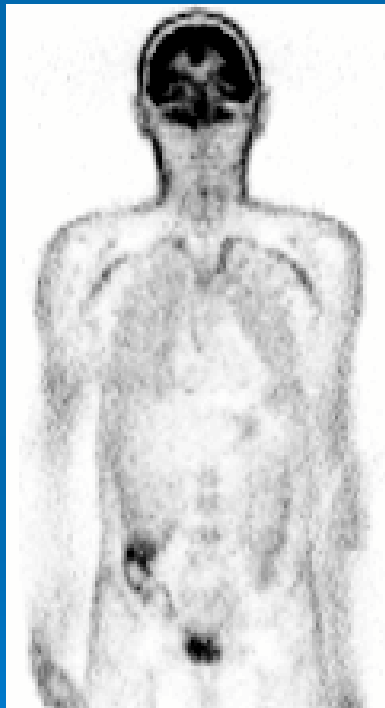
Diagnostic contribution of Gallium-67-scintigraphy and PET-scintigraphy in 40 patients with FUIO who underwent both examinations

Diagnostic category	PET scan			Galliumscan		
	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

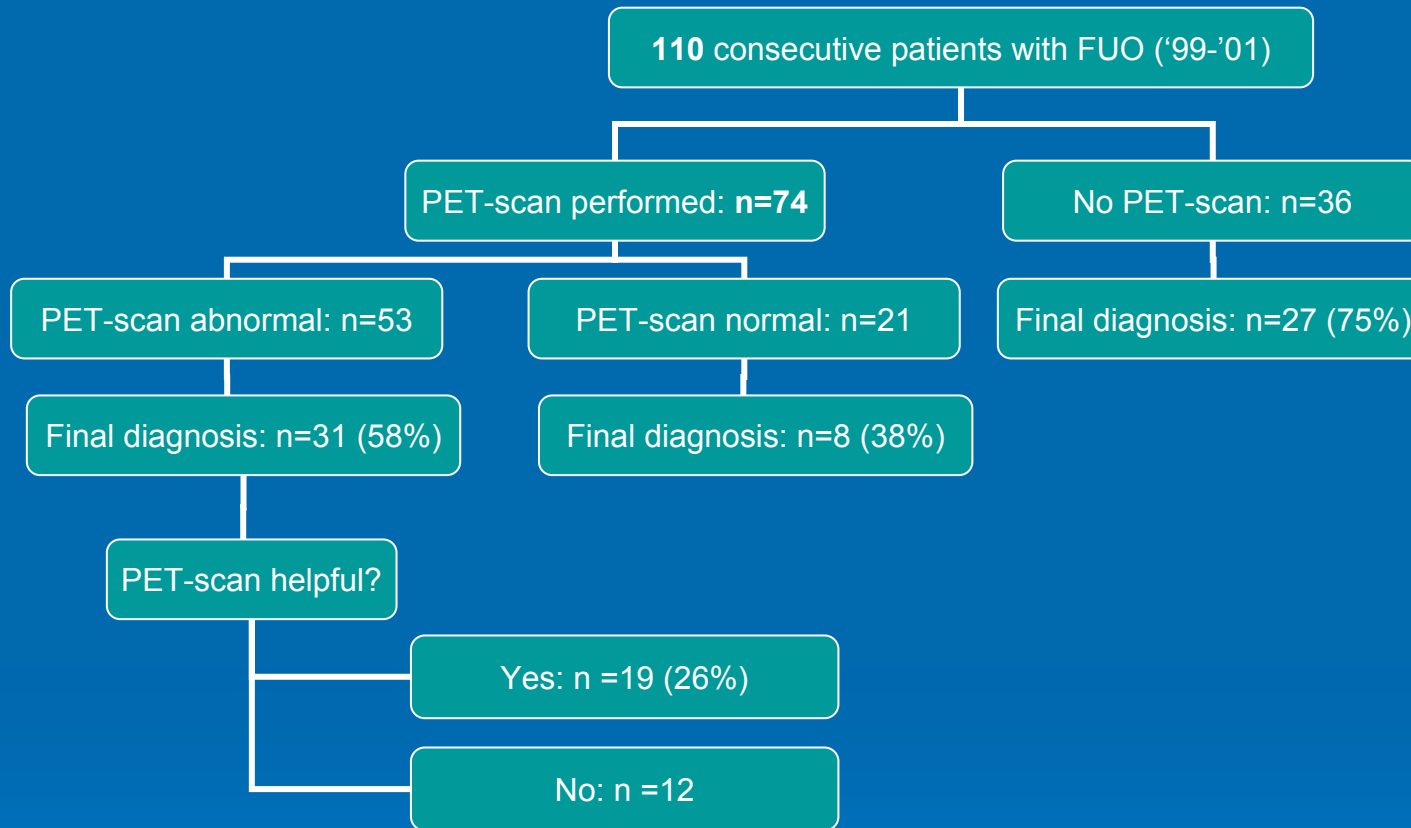
FDG-PET compared to Gallium:

- 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

Giant cell or temporal arteritis (Horton disease)



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



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

FDG-PET and FUO

Studies of FDG-PET in patients with FUO

Author	Blockmans	Lorenzen	Meller	Bleeker-Rovers	Buysschaert	Bleeker-Rovers
Period	1996–1998	1998–2000	1999–2000	1999–2002	1999–2001	2003–2005
Design	Prospective	Prospective	Prospective	Retrospective	Retrospective	Prospective
Total number	58	16	20	35	74	70
Diagnosed cases	38 (66) ^a	13 (81)	18 (90)	19 (54)	39 (53)	35 (50)
Scan abnormal	46 (79)	12 (75)	13 (65)	15 (43)	53 (72)	33 (47)
Scan helpful	24 (41)	11 (69)	11 (55)	13 (37)	19 (26)	23 (33)

^a Data represent number (percentage).

Diagnostic approach of FUO

staged approach (algorithm)

total body inflammation tracer scintigraphy

therapeutic trials

wait and see strategy

Therapeutic trials

- symptomatic antipyretic therapy: **NSAID !**, beware of hepatotoxicity particularly in case of Still disease
- therapeutic trial **only** in case of clinical deterioration
 - * **antibiotics**: - assess the effect of broad spectrum antibiotics and stop if no effect after 3 to 4 days !
 - consider the use of tetracyclines (or macrolides)
 - * **antituberculous agents**: clearly indicated
 - * **corticosteroids**: - **never (?) without antituberculous agents**
 - **do not start too early!**

Diagnostic approach of FUO

staged approach (algorithm)

total body inflammation tracer scintigraphy

therapeutic trials

wait and see strategy

Evolution of fever in surviving undiagnosed cases with F.U.O (n=49)

- Spontaneous resolution during or shortly after hospitalization
n=31
- Persisting or recurring fever (> 3 months after discharge)
n=18
 - “cured”: 10
 - 3 treated with corticosteroids
 - unresolved illness: 8
 - treated with corticosteroids (n=1)
 - treated with NSAID (n=6)
 - refused reinvestigation and died (n=1)

The future of the diagnostic approach of FUO

➤ Whole body MRI is the future

Computer time, acquisition time, reading time, costs are the limiting factors up till now

➤ MRI is useful for the diagnosis of infections (classical and hidden infections such as osteomyelitis, spondylodiscitis, infected vascular prosthesis,.....) tumours, large vessel vasculitis (temporal arteritis and Takayasu arteritis),, thyroiditis, hematomas,.....