NUCLEAR MEDICINE IMAGING IN FUO

Christophe Van de Wiele, M.D., Ph.D.
Department of Nuclear Medicine, University Hospital, Ghent, Belgium

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


- 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 outpatient visits
  - Nosocomial FUO
  - Neutropenic FUO
  - HIV-associated FUO


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**TABLE 1**

Classification of Fever of Unknown Origin (FUO)

<table>
<thead>
<tr>
<th>Category of FUO</th>
<th>Definition</th>
<th>Common etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Temperature &gt;38.3°C (100.9°F) Duration of ≥3 weeks Evaluation of at least 3 outpatient visits or 3 days in hospital</td>
<td>Infection, malignancy, collagen vascular disease</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>Temperature &gt;38.3°C Patient hospitalized ≥24 hours but no fever or incubating on admission Evaluation of at least 3 days</td>
<td>Clostridium difficile enterocolitis, drug-induced, pulmonary embolism, septic thrombophlebitis, sinusitis</td>
</tr>
<tr>
<td>Immune deficient (neutropenia)</td>
<td>Temperature &gt;38.3°C Neutrophil count ≤500 per mm³ Evaluation of at least 3 days</td>
<td>Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus</td>
</tr>
<tr>
<td>HIV-associated</td>
<td>Temperature &gt;38.3°C Duration of &gt;4 weeks for outpatients, &gt;3 days for inpatients HIV infection confirmed</td>
<td>Cytomegalovirus, Mycobacterium avium-intracellulare complex, Pneumocystis carinii pneumonia, drug-induced Kaposi's sarcoma, lymphoma</td>
</tr>
</tbody>
</table>

*HIV = human immunodeficiency virus.

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

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TABLE 2
Common Etiologies of Fever of Unknown Origin

<table>
<thead>
<tr>
<th>Infections</th>
<th>Autoimmune conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (especially pulmonary)</td>
<td>Adult SIV disease</td>
</tr>
<tr>
<td>Abdominal abscesses</td>
<td>Polyarthritis rheumatica</td>
</tr>
<tr>
<td>Pelvic abscesses</td>
<td>Temporal arthritis</td>
</tr>
<tr>
<td>Dental abscesses</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Rheumatoid fever</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Sjogren’s syndrome</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Systemic lupus, erythematous vasculitides</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Drug-induced fever</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>Complications from infection</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Focal fevers</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Neoplastic (alcoholic, granulomatous, or lupoid)</td>
</tr>
<tr>
<td>Chronic leukemia</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>Metastatic cancers</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Nodular Hyperplasia</td>
</tr>
<tr>
<td>Colon carcinoma</td>
<td></td>
</tr>
<tr>
<td>Hepatoma</td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
<td></td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Sarcomas</td>
<td></td>
</tr>
</tbody>
</table>

Big Three

Minor Three
CAUSES OF FUO: MOST FREQUENT

- Endocarditis, TB, abdominal abscesses, 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

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)

<table>
<thead>
<tr>
<th></th>
<th>Elderly(n=204)</th>
<th>Young(n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tuberculosis</td>
<td>20(10)</td>
<td>4(3)</td>
</tr>
<tr>
<td>- Abscess</td>
<td>25(12)</td>
<td>6(4)</td>
</tr>
<tr>
<td>- Endocarditis</td>
<td>14(7)</td>
<td>2(1)</td>
</tr>
<tr>
<td>- Viral</td>
<td>1(0.05)</td>
<td>8(5)</td>
</tr>
<tr>
<td>Tumour</td>
<td>38(19)</td>
<td>8(5)</td>
</tr>
<tr>
<td>SID’s</td>
<td>57(28)</td>
<td>27(17)</td>
</tr>
</tbody>
</table>

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

### NUCLEAR MEDICINE IMAGING IN FUO

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

• « pdc » = potentially diagnostic clues
  – Look for them
• If no pdc’s and/or directed examinations neg.
  – Staged approach
  – Total body inflammation/infection scan
  – Therapeutic trials
  – Wait and see strategy
Diagnostic approach of FUO

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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
  – Final diagnosis available in 68% (99pts)
  – 82 abnormal scans (57%), 42 of these were helpful (49%)
Total Body Inflammation/infection scan

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

$^{111}$In-oxine WBC in FUO

<table>
<thead>
<tr>
<th>Nb</th>
<th>Se</th>
<th>Spe.</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syrjala et al. 1987(JNM)</td>
<td>68</td>
<td>81%</td>
<td>90%</td>
</tr>
<tr>
<td>Schmidt et al. 1987(SJID)</td>
<td>32</td>
<td>?</td>
<td>100%</td>
</tr>
<tr>
<td>McSweeney et al. 1990(CIRad)</td>
<td>25</td>
<td>55%</td>
<td>79%</td>
</tr>
<tr>
<td>Kjaer et al. 2002(JNM)</td>
<td>31</td>
<td>75%</td>
<td>83%</td>
</tr>
</tbody>
</table>

$^{99m}$TC-antigranulocyte Ab scintigraphy

<table>
<thead>
<tr>
<th>Nb</th>
<th>Se</th>
<th>Spe.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker et al. 1993(EJNM)</td>
<td>34</td>
<td>40%</td>
</tr>
<tr>
<td>Meller et al. 1998(JNM)</td>
<td>51</td>
<td>helpfull in 27% of pts.</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Patients (n=292)</th>
<th>PET helpful (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meller et al</td>
<td>p</td>
<td>20 40 25 (15) 10 15 10</td>
<td>55 (PPV: 92; NPV: 75)</td>
</tr>
<tr>
<td>Blockmans et al</td>
<td>p</td>
<td>58 18 29 (14) 10 9 34</td>
<td>41 (PPV: 75; NPV: 75)</td>
</tr>
<tr>
<td>Lorenzen et al</td>
<td>r</td>
<td>16 19 50 (30) 6 6 19</td>
<td>60 (PPV: 92; NPV: 90)</td>
</tr>
<tr>
<td>Bleeker-Rovers et al</td>
<td>r</td>
<td>35 17 11 (3) 17 9 46</td>
<td>37 (PPV: 85; NPV: 90)</td>
</tr>
<tr>
<td>Kjer et al</td>
<td>p</td>
<td>19 26 16 (5) 6 16 36</td>
<td>16 (PPV: 85; NPV: 67)</td>
</tr>
<tr>
<td>Bylsma et al</td>
<td>r</td>
<td>74 9 5 (4) 16 19 51</td>
<td>26 (PPV: 75; NPV: 75)</td>
</tr>
<tr>
<td>Bleeker-Rovers et al</td>
<td>p</td>
<td>70 17 23 (6) 7 3 30</td>
<td>55 (PPV: 75; NPV: 90)</td>
</tr>
</tbody>
</table>

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

(Cum: 104/292 = 36%)


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)

118 consecutive patients with FUO (95-91)

PET-scan performed: n=74
PET-scan normal: n=21
Final diagnosis: n=27 (75%)

PET-scan abnormal: n=53
Final diagnosis: n=31 (58%)

PET-scan helpful?
Yes: n=19 (29%)
No: n=12

FDG-PET was helpful in 26% (19/74) of the patients with FUO
FDG-PET was helpful in 49% (31/63) of the patients with final diagnosis


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Table 3
Predictors of helpful FDG-PET

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

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

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>PET scan</th>
<th>Gallium scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal</td>
<td>contributory</td>
</tr>
<tr>
<td>infectious (n = 5)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>tumours (n = 3)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>multi-system diseases (n = 12)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>(vasculitis n = 4)</td>
<td>(0)</td>
<td>(4)</td>
</tr>
<tr>
<td>miscellaneous (n = 3)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>no diagnosis (n = 14)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>total (n = 40)</td>
<td>9</td>
<td>14</td>
</tr>
</tbody>
</table>

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

- 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
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

Total Body Inflammation/infection scan

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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 69-year-old man with episodic fever (38.3°C) since one year with right acetabulum, weight loss and vague discomfort in the hips.

ESR was 53 mm/h (normal <10 mm/h) and CRP 69 mg/l (normal <5 mg/l).

*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

[Imagery of aortic inflammation with medical diagrams]
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  – Wait and see strategy
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


Thank you for your attention