Fever of Unknown Origin

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Fever of unknown origin (FUO)

• Common problem in general internal medicine

• In up to 50% NO DIAGNOSIS after extensive diagnostic tests

• Most frequent diagnoses:
  • Infection
  • Non-infectious inflammatory diseases
  • Malignancy
Definition

- Illness > 3 weeks duration
- Fever > 38.3°C (101°F) on at least two occasions
- No diagnosis after certain diagnostic tests (laboratory tests, urinalysis, chest X-ray, abdominal ultrasound, 3 blood cultures, urine culture, tuberculin skin test)
- Exclusion of immunocompromised patients
CMS Denies New PET Coverage for Infection, Inflammation

The Centers for Medicare and Medicaid Services (CMS) released on March 19 a Decision Memorandum stating that “based upon our review CMS has determined that the evidence is inadequate to conclude that FDG PET for chronic osteomyelitis, infection of hip arthroplasty, and fever of unknown origin improves health outcomes in the Medicare populations.” This decision, which signaled continued non-coverage for $^{18}$F-FDG PET in these indications, also included specific language excluding coverage for these indications under the Coverage with Evidence Development paradigm on which the National Oncologic PET Registry is based (see Newsline article, above).

The final ruling was not unexpected and followed a December 2007 CMS recommendation to decline reimbursement. At that time, the agency asked for the submission of new evidence accrued since the original formal request for coverage of these indications was received in June 2007 from Abass Alavi, MD, chief of the nuclear medicine section at the University of Pennsylvania (Philadelphia), and Javad Parviz, MD, associate professor of orthopedic surgery at Thomas Jefferson University (Philadelphia).

The Decision Memorandum (www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=207&c) summarized the evidence presented, criteria used to determine coverage status, and reasons for declining coverage. Language in the Decision Memorandum indicated that negative factors in the decision included the absence of “any systematic reviews” in the literature evaluating the use of $^{18}$F-FDG PET for the requested indications, a paucity of data supporting the ability of PET imaging to improve treatment or enhance long-term outcomes, and the absence of evidence-based guidelines for the use of PET in the requested indications. Articles submitted for support of expanded approval were criticized for small sample sizes and methodologic and statistical flaws.

A “lack of interest” was also cited by CMS as a negative factor: “...we note the marked paucity of expressed interest on this issue by practicing orthopedic surgeons or their professional societies. Similarly we note the lack of expressed interest from those physicians, generally infectious disease specialists, who would routinely be asked to consult in cases of fever of unknown origin. This leads us to reasonably determine that the interest in the use of PET for these indications is narrow and does not apparently include the physicians who routinely manage the care of beneficiaries who have these conditions.”

Centers for Medicare and Medicaid Services
Radiology in FUO

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Helpful</th>
<th>False positive</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>6 (8%)</td>
<td>8 (11%)</td>
<td>60% (26-88%)</td>
<td>87% (77-94%)</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>6 (10%)</td>
<td>18 (31%)</td>
<td>86% (42-100%)</td>
<td>65% (50-78%)</td>
</tr>
<tr>
<td>Abdominal CT</td>
<td>12 (20%)</td>
<td>17 (29%)</td>
<td>92% (64-100%)</td>
<td>63% (48-77%)</td>
</tr>
<tr>
<td>Chest CT</td>
<td>9 (20%)</td>
<td>8 (17%)</td>
<td>82% (48-98%)</td>
<td>77% (60-90%)</td>
</tr>
</tbody>
</table>

Bleeker-Rovers et al., Medicine (Baltimore) 2007;86:26-38
FDG-PET vs. CT/MRI in FUO

**Advantages of FDG-PET:**
- Less disturbance by metallic implants
- Whole body screening
- Absence of contrast-related side-effects
- Higher positive and negative predictive values

**Disadvantages:**
- More limited anatomical information: not with integrated PET-CT
- Costs
## FDG-PET in FUO

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Study design</th>
<th>helpful</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meller (2000)</td>
<td>Prospective (n=20)</td>
<td>55%</td>
<td>92%</td>
<td>75%</td>
</tr>
<tr>
<td>Blockmans (2001)</td>
<td>Prospective (n=58)</td>
<td>41%</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Lorenzen (2001)</td>
<td>Retrospective (n=16)</td>
<td>69%</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>Bleeker-Rovers (2004)</td>
<td>Retrospective (n=35)</td>
<td>37%</td>
<td>87%</td>
<td>95%</td>
</tr>
<tr>
<td>Kjaer (2004)</td>
<td>Prospective (n=19)</td>
<td>16%</td>
<td>30%</td>
<td>67%</td>
</tr>
<tr>
<td>Buysschaert (2004)</td>
<td>Prospective (n=74)</td>
<td>26%</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Bleeker-Rovers (2007)</td>
<td>Prospective, multicenter (n=70)</td>
<td>33%</td>
<td>70%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Overall helpfulness corrected for study population: 36%!
FDG-PET vs. $^{111}$In/$^{99m}$Tc-leukocyte/$^{67}$Ga

**Advantages of FDG-PET:**
- No handling of potentially infected blood products
- Lower radiation burden
- Shorter timespan between injection and diagnosis
- Higher resolution
- High accuracy in the central skeleton
- Sensitivity in chronic low grade infections
- Suitable for diagnosis of malignancy and vasculitis
FDG-PET vs. $^{67}$Ga scintigraphy

Meller et al.¹:
- 18 patients with FUO: FDG-PET and $^{67}$Ga scintigraphy
- Higher accuracy of FDG-PET

Blockmans et al.²:
- 40 patients with FUO: FDG-PET and $^{67}$Ga scintigraphy
- FDG-PET helpful: 35%
- $^{67}$Ga helpful: 25%
- Higher accuracy of FDG-PET

²Blockmans et al., CID 2001;32:191-6
FDG-PET vs. $^{67}$Ga scintigraphy

Adnexitis of the right pelvis:
- FDG-PET: true positive
- $^{67}$Ga: false negative

Psittacosis:
- FDG-PET: true positive
- $^{67}$Ga: true positive

FDG-PET vs. leukocyte scintigraphy

Kjaer et al.:
- 19 patients with FUO: FDG-PET and $^{111}$In-leukocyte scintigraphy
- FDG-PET: helpful: 16%
- Leukocyte scanning: helpful 26%
- More false positives in FDG-PET
- But:
  - Selected patient population (department of infectious diseases)
  - No follow up in patients with presumed false positive FDG-PET
FDG-PET in FUO

- Prospective trial in 6 hospitals (1 university and 5 community)
- Structured diagnostic protocol
- 75 eligible patients, 70 recruited:
  - final diagnosis in 50%
  - 33% FDG-PET clinically helpful, only when ESR / CRP ↑
  - FDG-PET better in continuous fever than in periodic fever
  - negative predictive value 95%, positive predictive value 70 %

Bleeker-Rovers et al. Medicine (Baltimore) 2007; 86: 26-38
FDG-PET in FUO

- Consider FDG-PET in patients with ESR / CRP ↑ and continuous fever
- Periodic fever: lower yield, but exclusion of focal disease
- FDG-PET seems appropriate when performed early to guide intelligent further testing
- In case of normal FDG-PET results, many follow-up tests can be avoided in these patients
a 73-year-old man with FUO

No diagnosis after chest X-ray, abdominal ultrasound, colonoscopy, In-111-leukocyte-scan

**Diagnosis**: septic thrombophlebitis of the portal vein (black arrow) and small liver abscesses (red arrow)
a 70-year-old woman with fever and backache

FDG-PET: FDG-uptake in L2-L3 suggesting spondylodiscitis

MRI: compatible with spondylodiscitis L2-L3

Diagnosis: spondylodiscitis due to *Candida albicans*
A 76-year-old woman with fever of unknown origin

No diagnosis after:
• Chest X-ray
• abdominal and thoracic CT-scans
• MRI of the spine
• bone scan
• $^{111}$indium-leukocyte scan
• gastroscopy, colonoscopy and bronchoscopy
• duodenum, liver, bone and temporal artery biopsies

Diagnosis: malignant B-cell lymphoma
A 61-year-old woman with periodic fever

- periodic fever since 6 years, night sweats, CRP 20-60
- Extensive analysis in 2 other hospitals, abdominal CT normal

**Diagnosis:** diverticulitis
A 62-year-old woman with FUO

- fever since 5 weeks, weight loss
- painful left temporal artery
- ESR 122
- temporal artery biopsy: normal

**Diagnosis:** large vessel vasculitis

- Prednison: complete resolution of symptoms
A 65-year-old man with FUO

No diagnosis after chest X-ray, abdominal CT, colonoscopy

Diagnosis after FDG-PET and biopsy: M. Hodgkin
FDG-PET for detection of metastatic infectious foci

Number of patients having metastatic foci
Study patients (n=115) 78 (68%)
Control patients (n=230) 82 (36%)

Test characteristics FDG-PET regarding complicating metastatic foci
Sensitivity 100%
Specificity 87%
Positive predictive value 89%
Negative predictive value 100%
FDG-PET for detection of metastatic infectious foci

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Study patients (n=115)</th>
<th>Control patients (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>21/ 18%</td>
<td>19/ 8.2%*</td>
</tr>
<tr>
<td>Endovascular</td>
<td>20/ 17% (12)</td>
<td>9/ 3.9%*</td>
</tr>
<tr>
<td>Lung</td>
<td>12/ 10% (6)</td>
<td>8/ 3.5%*</td>
</tr>
<tr>
<td>Liver</td>
<td>1/ 0.9%</td>
<td>1/ 0.4%</td>
</tr>
<tr>
<td>Spleen</td>
<td>1/ 0.9% (1)</td>
<td>0</td>
</tr>
<tr>
<td>Arthritis</td>
<td>10/ 8.7% (3)</td>
<td>28/ 12%</td>
</tr>
<tr>
<td>Spondylodiscitis</td>
<td>11/ 9.6% (8)</td>
<td>10/ 4.3%</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>6/ 5.2% (1)</td>
<td>3/ 1.3%</td>
</tr>
<tr>
<td>Psoas abscess</td>
<td>3/ 2.6% (2)</td>
<td>1/ 0.4%</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>11/ 9.6% (4)</td>
<td>12/ 5.2%</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>11/ 9.6% (3)</td>
<td>7/ 3.0%*</td>
</tr>
<tr>
<td>Eye</td>
<td>3/ 2.6%</td>
<td>0*</td>
</tr>
<tr>
<td>Joint prosthesis</td>
<td>9/ 7.8% (3)</td>
<td>5/ 2.2%*</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>4/ 3.5% (1)</td>
<td>6/ 2.6%</td>
</tr>
<tr>
<td>Kidney</td>
<td>1/ 0.9%</td>
<td>4/ 1.7%</td>
</tr>
</tbody>
</table>

In 30 study patients and 22 controls more than 1 metastatic foci were present. Number of foci first detected by FDG-PET are shown between brackets. * p=<0.05
FDG-PET for detection of metastatic infectious foci

<table>
<thead>
<tr>
<th></th>
<th>Study patients</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total group (3 mo)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>72 (62.6%)</td>
<td>151 (65.6%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>3 (2.6%)</td>
<td>17 (7.4%)</td>
</tr>
<tr>
<td>Persisting infection</td>
<td>21 (18.2%)</td>
<td>3 (1.3%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>19 (16.6%)</td>
<td>59 (25.7%)</td>
</tr>
<tr>
<td><strong>Total group (6 mo)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>77 (67%)</td>
<td>147 (64%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Persisting infection</td>
<td>7 (6.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Mortality</td>
<td>21 (18.2%)</td>
<td>71 (30.8%)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>10 (8.7%)</td>
<td>12 (5.2%)</td>
</tr>
<tr>
<td><strong>Total group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission days (mean)</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Admission &lt;15 days</td>
<td>34 (30%)</td>
<td>101 (44%)</td>
</tr>
<tr>
<td>Duration of therapy (mean)</td>
<td>52</td>
<td>25</td>
</tr>
<tr>
<td>Therapy &lt;15 days</td>
<td>29 (25%)</td>
<td>115 (50%)</td>
</tr>
</tbody>
</table>

*Six months follow-up was not available in all patients.
Conclusions

• FDG-PET first choice nuclear medicine technique in FUO
• FDG-PET not useful in patients with repeatedly normal CRP and ESR
• Periodic fever: FDG-PET during febrile episode
• Structured diagnostic protocol is advised
Diagnostic protocol

- History and physical examination
- Obligatory investigations
- Stop or replace medication to exclude drug fever
- Exclude manipulation with thermometer

Bleeker-Rovers et al. Medicine (Baltimore) 2007; 86: 26-38
Diagnostic protocol

PDC: potentially diagnostic clue

[1] PDCs present

- continuous fever
  - guided diagnostic tests
    - DIAGNOSIS
    - NO DIAGNOSIS to [II]

- recurrent fever
  - search for specific syndromes
    - DIAGNOSIS
    - NO DIAGNOSIS to [II]

history and physical examination
obligatory investigations
stop or replace medication to exclude drug fever
exclude manipulation with thermometer

Bleeker-Rovers et al. Medicine (Baltimore) 2007; 86: 26-38
Diagnostisch protocol

- **History and physical examination**
- **Obligatory investigations**
- **Stop or replace medication to exclude drug fever**
- **Exclude manipulation with thermometer**

### [I] PDCs present

- **Continuous fever**
  - **Guided diagnostic tests**
  - **Diagnosis**
  - **No diagnosis to [II]**

- **Recurrent fever**
  - **Search for specific syndromes**
  - **Diagnosis**
  - **No diagnosis to [II]**

### [II] PDCs absent or misleading

- **First level investigation: cryoglobulin**
- **No diagnosis**
- **Diagnosis**

- **Follow-up for new PDCs, consider NSAID**
- **Stable condition further diagnostic tests, consider therapeutic trial**
- **Deterioration**

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Bleeker-Rovers et al. Medicine (Baltimore) 2007; 86: 26-38
Diagnostic protocol

1. PDCs present
   - continuous fever
     - guided diagnostic tests
       - DIAGNOSIS
       - NO DIAGNOSIS to [ II ]
   - recurrent fever
     - search for specific syndromes
       - DIAGNOSIS
       - NO DIAGNOSIS to [ II ]

2. PDCs absent or misleading
   - first level investigation: cryoglobulin
     - NO DIAGNOSIS
     - DIAGNOSIS
       - FDG-PET-scan
         - FDG-PET abnormal
           - conventional diagnostic tests to confirm abnormality
             - DIAGNOSIS
             - NO DIAGNOSIS
               - stable condition
                 - follow-up for new PDCs, consider NSAID
               - deterioration
                 - further diagnostic tests, consider therapeutic trial
         - FDG-PET normal
           - second level investigations
             - DIAGNOSIS
             - NO DIAGNOSIS
               - stable condition
                 - follow-up for new PDCs, consider NSAID
               - deterioration
                 - further diagnostic tests, consider therapeutic trial

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