Diagnostic approach to fever of unknown origin

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FuO

- Definitions
- Causes
- Diagnostic approach
- Prognosis
- Conclusion

Definition of FuO

From the original to the contemporary

Not every fever with unclear cause or source = FuO!

- Ongoing and enigmatic febrile illnesses
- “These cases are encountered once or twice a month at teaching hospitals.”

**FUO: 1961 definition**

1. Illness >3 weeks.
2. Fever >38.3°C (>101°F), on several occasions.
3. Diagnosis uncertain after 1 week of study in hospital.

RT Petersdorf 1926-2006
PB Beeson 1908-2006


**FUO definition by Durack and Street**

- Classical FUO
  - Duration >3 weeks
  - Fever >38.3°C
  - Diagnosis uncertain despite appropriate investigations, after ≥3 outpatient visits or ≥3 days in hospital
- Nosocomial FUO
- Neutropenic FUO
- HIV-associated FUO

D. T. Durack & A. C. Street.

**FUO: 1961 definition**

1. Illness >3 weeks.
   → Tends to eliminate self-limited infectious diseases.
2. Fever >38.3°C (>101°F), on several occasions.
   → Eliminates the entity of ‘habitual hyperthermia’
3. Diagnosis uncertain after 1 week of study in hospital.
   → Time interval to allow completion of laboratory studies (e.g., bacteriologic and serologic tests, radiologic examinations, skin tests,...)
• Nosocomial FUO
  - Infections (respiratory, urinary, wound, catheter, sinusitis, Clostridium difficile, …)
  - Drug fever
• Neutropenic FUO
  - Infections (bacterial, fungal, viral, parasитаir)
  - Malignancy
• HIV-associated FUO
  - Infections
  - Drug fever
  - Malignancy

CONTEMPORARY DEFINITION OF CLASSICAL FUO
1. Illness of >3 weeks duration
2. Temperature ≥38.3°C - or lower with lab signs of inflammation - on several occasions.
3. No diagnosis after initial diagnostic investigation
4. Exclusion of nosocomial fever and severe immunocompromise

MINIMUM DIAGNOSTIC EVALUATION
to qualify as FUO

- Comprehensive history (including travel history, risk for venereal diseases, hobbies, pet animals and birds, etc.)
- Comprehensive physical examination (including temporal arteries, rectal digital examination, etc.)
- Routine blood tests (CBC, including differential, ESR or CRP, electrolytes, renal and hepatic tests, CK and LDH)
- Microscopic urinalysis
- Cultures of blood, urine other normally sterile compartments as indicated, e.g., joints, pleura, cerebrospinal fluid
- Chest radiograph
- Abdominal (including pelvic) ultrasonography
- Antinuclear and antineutrophilic cytoplasmic antibodies, rheumatoid factor
- Tuberculin skin test
- Serological tests directed by local epidemiological data
- Further evaluation directed by abnormalities detected by above tests, e.g.
  - HIV antibodies depending on clinical history
  - CMV-IgM and EBV serology in case of abnormal differential WBC count
  - Abdominal or chest helical CT scan
  - Echocardiography in case of cardiac murmur

Causes of FUO

- Diagnostic categories
- Common causes
- Subpopulations

Knowledge of the causes and the spectrum

“FUO defies simplification. Reported causes exceed 200, and fall into diverse sub-specialty categories. There are no algorithms and few clues that reliably suggest or exclude particular diagnoses. The clinician must rely on very careful evaluation and detailed knowledge of a wide variety of diseases.”


FUO: diagnostic categories

1. Infections
2. Malignancies
3. Non-infectious inflammatory disorders (NIID)
   a) Connective tissue diseases
   b) Vasculitides
   c) Granulomatous disorders
4. Miscellaneous disorders
5. Undiagnosed cases.

Common causes:

“Most patients with FUO are not suffering from unusual diseases; instead they exhibit atypical manifestations of common illnesses.”

Most common causes

14 disorders — 2/3 of the diagnoses

1. Infections:
   - Endocarditis
   - Tuberculosis
   - Abdominal abscesses
   - EBV/CMV infections

2. Malignancies:
   - Lymphoma
   - Leukemia

3. Non-infectious inflammatory disorders
   - Adult-onset Still disease
   - Systemic lupus erythematosus
   - Polyarteritis nodosa
   - Gout
   - Crohn disease

4. Miscellaneous disorders
   - Habitual hyperthermia
   - Drug fever
   - Subacute thyroiditis


Diagnostic spectrum

Depends on:
- Time
- Region
- Age
- Fever pattern (episodic vs continuous)

Time matters: the spectrum evolves

Are we losing it?

Apparent loss of diagnostic yield

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

Munne et al. Arch Int Med 2003;163:545
Region matters: Causes of FUO in adults

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Country</th>
<th>Number</th>
<th>Causes (%)</th>
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<tbody>
<tr>
<td>2003</td>
<td>Vanderschueren et al.</td>
<td>Belgium</td>
<td>223</td>
<td>Infections 14</td>
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<tr>
<td></td>
<td>Zamir et al</td>
<td>Israel</td>
<td>101</td>
<td>Tumours 10</td>
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<tr>
<td></td>
<td>Baicus et al</td>
<td>Romania</td>
<td>164</td>
<td>NIID'S 20</td>
</tr>
<tr>
<td>2003</td>
<td>Öztürk</td>
<td>Turkey</td>
<td>145</td>
<td>Miscellaneous 10</td>
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</table>

Age matters

<table>
<thead>
<tr>
<th></th>
<th>Elderly (n = 204)</th>
<th>Young (n = 152)</th>
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<tbody>
<tr>
<td>Infection</td>
<td>72 (35)</td>
<td>33 (22)</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 infections</td>
<td>1 (0.5)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>38 (19)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>NIID</td>
<td>57 (28)</td>
<td>27 (17)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>17 (8)</td>
<td>39 (26)</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>18 (9)</td>
<td>45 (29)</td>
</tr>
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</table>

Periodicity of fever matters: Episodic versus continuous FUO

<table>
<thead>
<tr>
<th></th>
<th>Recurrent Fever (n = 45) (%)</th>
<th>Continuous Fever (n = 154) (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>4 (8.8)</td>
<td>41 (26.8)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Tumour</td>
<td>2 (4.4)</td>
<td>12 (7.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Multisystem disease</td>
<td>4 (8.8)</td>
<td>38 (25.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Drug-related fever</td>
<td>1 (2.2)</td>
<td>5 (3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Factitious fever</td>
<td>1 (2.2)</td>
<td>6 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Habitual hyperthermia</td>
<td>0</td>
<td>5 (3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1 (2.2)</td>
<td>19 (12.9)</td>
<td>NS</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>23 (51.0)</td>
<td>28 (18.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Knackert et al. Medicine 1993, 72, 184.
**Initial approach**

- Review the 'minimal diagnostic approach'
- Rule out the 'little 3'

**MINIMUM DIAGNOSTIC EVALUATION**

to qualify as FUO

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  - HIV antibodies depending on detailed history
  - CMV-IgM and EBV serology in case of abnormal differential WBC count
  - Malignancy or chest helical CT scan
  - Echocardiography in case of cardiac murmur
  - etc.

**Causes of FUO: big & little 3**

- Infections
- Malignancies
- NIID’s
- Drug fever
- Factitious fever
- 'Habitual hyperthermia'

**Rule out the little 3**

- Rule out factitious fever: document the fever.
- Rule out habitual hyperthermia: temperature chart & settings
- Rule out drug fever: stop all nonessential medications
"Look where the money is!"

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*do not carry out a battery of "routine" examinations in a conventional sequence*

What if ‘potentially diagnostic clues’ are absent or prove to be misleading?

- Total body inflammation tracer
- Therapeutic trials
- Wait and see

‘whole body inflammation tracer scintigraphy’

- FDG-PET scintigraphy: Large vessel vasculitis
- FDG-PET scintigraphy: Foreign body infection (osteosynthesis)
Beware of selective testing

- Indicated in case of individual suspicion, to confirm the diagnosis (biopsy, culture); not as a routine ('fishing expedition')
  - Endoscopic techniques (e.g., GI, bronchoscopy)
  - Selective radiographs (e.g., of teeth, sinuses, sacroiliac joints)
  - Contrast studies (e.g., GI, arteriography)
  - Invasive studies (mediastinoscopy, thoracoscopy, laparoscopy)
  - Blind punctures (bone marrow, liver, lumbar puncture)
- Consider less invasive techniques (e.g., EBUS, echoendoscopy)
- Exception to the rule: temporal artery biopsy in 50+

Therapeutic trials in classic FUO

- Therapeutic trials are seldom diagnostically rewarding and tend to obscure rather than to illuminate.
- Symptomatic: NSAID
- Therapeutic trial to be considered in case of deterioration
  * Antibiotics:
    - Broad spectrum antibiotics: stop if no defervescence after 3 days
    - Consider tetracyclines (or macrolides)
  * Antituberculosis therapy: strongly consider in case of clinical deterioration
  * Corticosteroids:
    - Do not start too early
    - Consider adding antituberculosis therapy.

Approach to FUO

- 'Total body inflammation tracer scintigraphy'
- Therapeutic trails
- Wait-and-see-strategy

Prognosis of classical FUO

- ~ Underlying disease
  - e.g.: long-term survivors
    - 9% of patients with malignancies
    - 78% of patients with infections
    - 88% of patients in other categories
  Larson et al. Medicine 1982;61:269
- Hematological malignancies: 12% of diagnoses ≠ 60% of deaths
  Vanderschueren et al. Arch Intern Med 2003;163:1033
- Most patients who left hospital without diagnosis did remarkably well.
Evolution of fever in FUO patients discharged without diagnosis (n=49)

- Spontaneous resolution during or shortly after hospitalisation: n=31
- Continuous or recurrent fever (> 3m after discharge): n=18
  - "cured": 10
    - 3 treated with corticosteroids
    - Persistent fevers: 8
- Treated with corticosteroids (n=1)
- Treated with NSAIDs (n=6)
- Refused new investigation and died (n=1)


"... many patients are placed in the FUO category because the attending physicians overlook, disregard or reject an obvious clue. No malice is implied by this observation; it simply means that clinicians, being human instruments, are far from perfect.

In order to mitigate the frequency and magnitude of these human errors, clinicians have to work that much harder. This means going over the patient again and again, repeating the history and physical examination, reviewing the chart, discussing the problem with colleagues in order to glean new ideas, and spending time in quiet contemplation of the clinical enigma.

The approach to the patient with FUO is not to bring on yet another barrage of tests, some of which might be painful and all of which probably are expensive, nor to dose the patient with antimicrobials or to subject him to exploratory surgery, in the absence of clinical clues and only as a last resort. There is no substitute for observing the patient, talking to him and thinking about him."


Conclusion

- FUO remains a challenge
  - Some fevers remain of unknown origin and represent a source for humility on the part of the diagnostician, but may at the same time serve as an impetus for continued research.
- Keep in mind
  - The diagnostic spectrum
  - Local epidemiology
  - 'Big three' - 'Little three'
  - Common causes are frequent.
- 'Go where the money is'.
  When 'potentially diagnostic clues' are absent or misleading, 'return to basics', 'wait and see' and/or consider an 'inflammation tracer'.