FEVER OF UNKNOWN ORIGIN

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1961 definition

1. **Ilness> 3 weeks**

2. **Fever>38.3°C (>101°F), on several occasions**

3. **Diagnosis uncertain after 1 week of study in hospital**

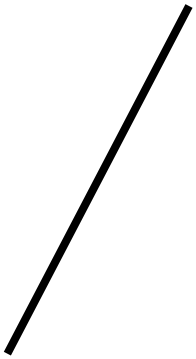
Petersdorf, Beeson. Medicine. 1961.

fièvre au long cours

Durack & Street Definition

- Classical FUO
  - >3 weeks
  - ≥ 38.3 °C
  - Diagnosis uncertain despite appropiate investig after ≥3 outpatient visits or ≥3 days in hospital

- Nosocomial FUO
- Neutropenic FUO
- HIV-associated FUO



early empiric antimicrobial therapy

Durack & Street, 1991

Definition of FUO today

- > 3 weeks
- ≥ 38.3 °C, on several occasions
- No diagnosis after initial diagnostic investigation
- Exclusion of nosocomial fever and severe immunocompromise

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)

Mourad et al.
A Comprehensive Evidence-Based Approach to Fever of Unknown Origin.
Arch Intern Med. 2003

"FUO defies simplification. Reported causes exceed 200, and fall into diverse sub-speciality 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."

Arnow, Flaherty. Lancet 1997.

Bottom line

- Thorough history taking and continuous observation is extremely important; repeat history after the physical if there are no clues. SORT C
- Exclude factitious fever and drug-related fever first. SORT C (little three)
- **Infections** (extrapulmonary tuberculosis most common) followed by **neoplasms** and **multisystem disease** are the most common causes of fever of unknown origin (FUO). SORT B **(big three)**
- In elderly patients, consider temporal arteritis and adult-onset Still's disease. SORT B

Stevceva. Essential Evidence Plus, 2010.

- 49% of patients received a diagnosis
  - infectious (16%)
  - neoplasia (7%)
  - noninfectious inflammatory disorders (22%)
  - miscellaneous causes (4%)
- No cause of the fever was identified in 51% of the patients.

Bleeker-Rovers, 2007.

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
   - Polymyalgia rheumatica – giant cell arteritis
   - Sarcoidosis
   - Crohn disease
4. **Miscellaneous disorders**
   - Habitual hyperthermia
   - Drug fever
   - Subacute thyroiditis

Vanderschueren. Arch Intern Med 2003;163:1033.

Diagnostic categories

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

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

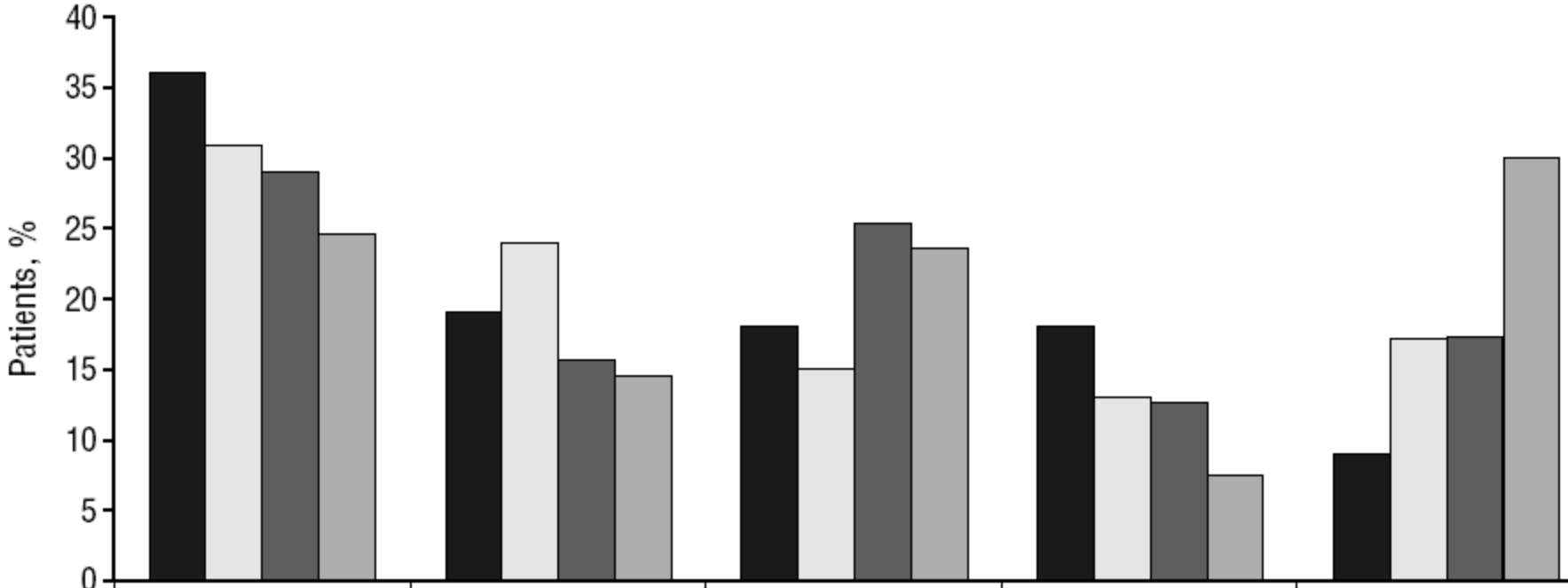
Petersdorf , Beeson. Medicine 1961

Diagnostic spectrum

Depends on:

- Time
- Region
- Age
- Fever pattern (episodic vs continuous)

Time



	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 Intern Med. 2003***

Region matters:
Causes of FUO in adults

Year Author	2003 Vanderschueren et al.	2003 Zamir et al	2003 Baicus et al	2003 Öztürk
Country	Belgium	Israël	Romania	Turkey
Number	223	101	164	145
Causes (%)				
Infections	14	54	45	64
Tumours	10	7	25	5
NIID'S	20	2	18	16
Miscellaneous	10	2	4	1
Undiagnosed	44	32	7	12

S.Vanderschueren. **DIAGNOSTIC APPROACH TO FEVER OF UNKNOWN ORIGIN, 2009**

Continuous/episodic

- Infection: continuous
- Systemic disease: continuous
- No diagnosis: episodic

Knockaert, 1993

- Probability not to reach a diagnosis:
  - periodic, no anemia, normal protein electrophoresis

de Kleijn, 1997

Infections

- As duration of fever increases, infectious etiology decreases
- Malignancy, factitious fevers and granulomatosis are more common in patients with prolonged FUO.

History

- Recent travel
- Exposure to pets and other animals
- Sexual history
- Work environment
- Contact with other people with similar symptoms
- Family history
- Past medical history list of medications
  - Include OTC

Physical Exam

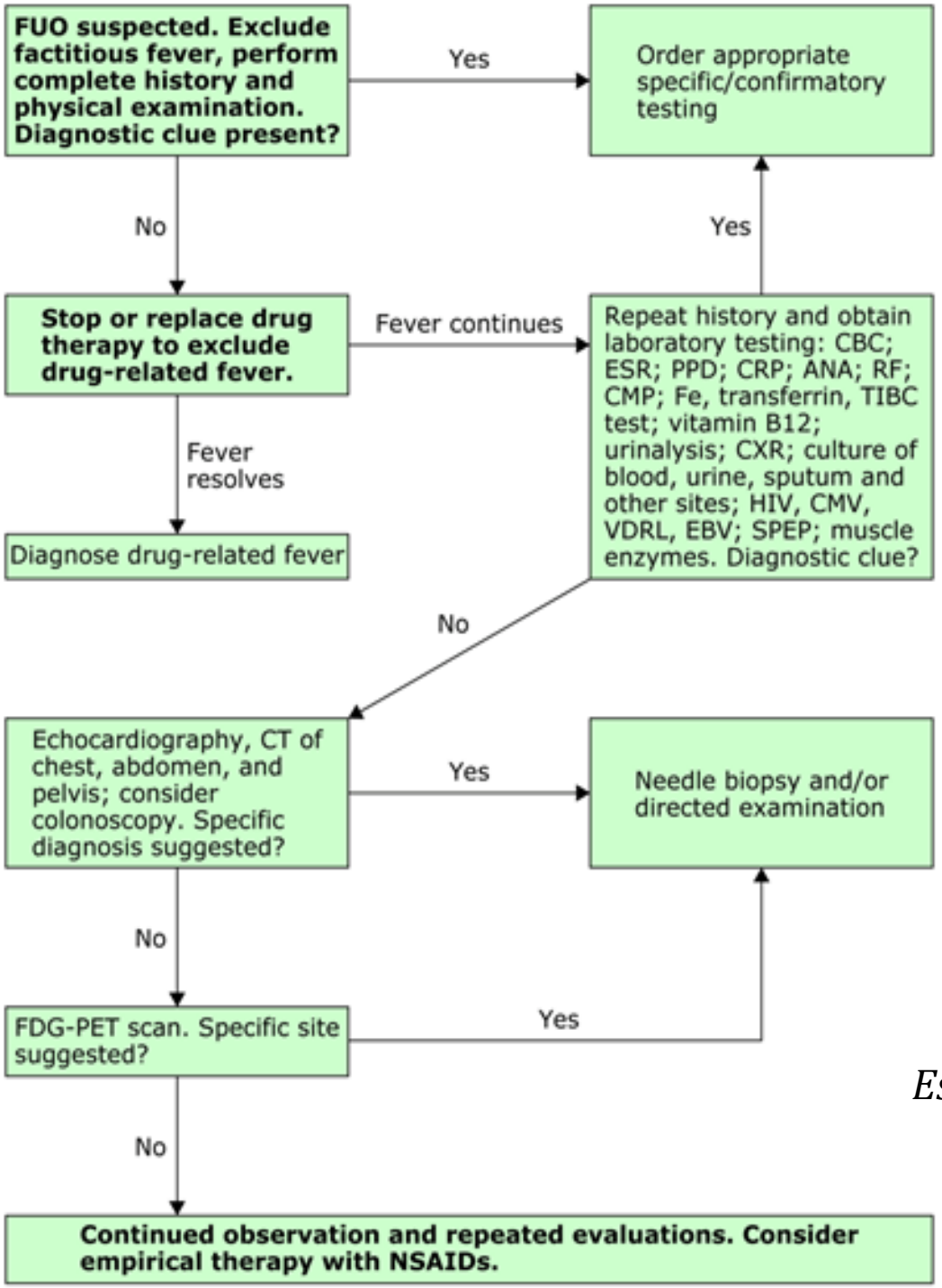
- Skin
- Mucous membranes
- Lymphadenopathy
- Organomegaly

Diagnosis

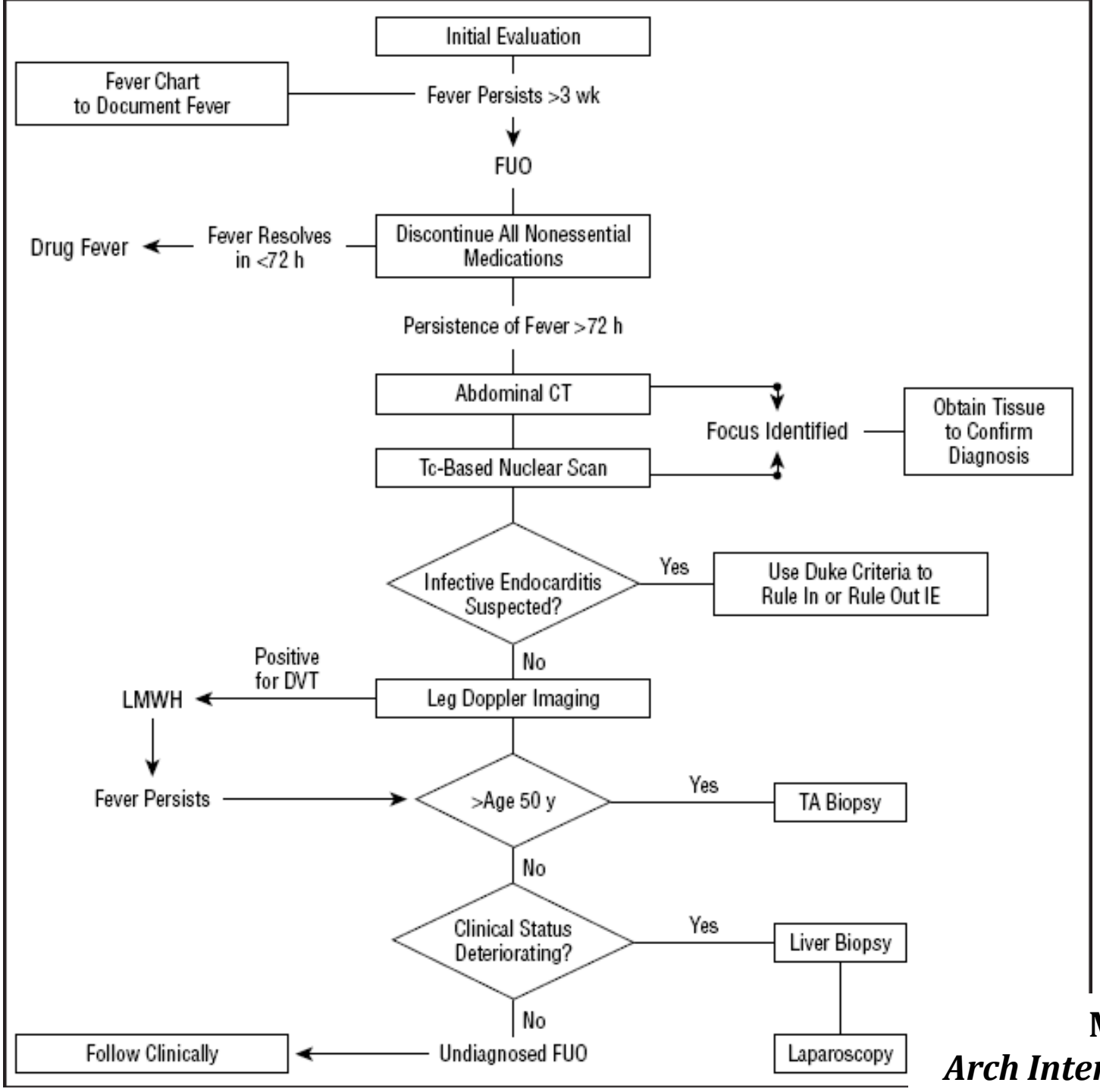
- A cost-effective individualized approach is essential in the evaluation of these patients to prevent performing inappropriate tests.

- Sutton's law: "Look were the money is"

- Potential diagnostic clues



Stevceva.
Essential Evidence Plus, 2010



Mourad et al.
Arch Intern Med. 2003

Diagnostic clues absent or misleading

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

Selective tests

- 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., endobronchial US, echoendoscopy)
- Exception to the rule: temporal artery biopsy in 50+

Vandershueren, 2009

- ESR>100 mm/h: LR+=19 for infection

Fincher, Arch Intern Med 1986

- Infection, 2 of 3:
  - PCR>60mg/l
  - Ferritin<500mcg/l,
  - Eosinophils<40/mm3

Efsathiou, Eur J Int Med 2010

Therapeutic trials

Therapeutic trails 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.

Vandershueren, 2009

Prognosis

- Depend on underlying diagnosis
- Pts without diagnosis: good pronosis
- *Knockaert, Arch Int Med 1996*: 49 pts
  - 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 douse 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."

Larson EB et al. Medicine 1982; 61:269-292.

Conclusions

- FUO remains a challenge
- 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'.