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."

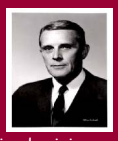
Arnow, Flaherty. Lancet 1997; 350: 575-580

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



Petersdorf RT, Beeson PB. Fever of unexplained origin: Report on 100 cases. Medicine 1961;40:1-30.

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,…)

FUO definition by Durack and Street

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

*D.T. Durack & A.C. Street. Curr Clin Topics Infect Dis **1991**; 11, 35-51.*

- **Nosocomial FUO**
  - Infections (respiratory, urinary, wound, catheter, sinusitis, Clostridium difficile, …)
  - Drug fever
- **Neutropenic FUO**
  - Infections (bacterial, fungal, viral, parasitic)
  - Malignancy
- **HIV-associated FUO**
  - Infections
  - Drug fever
  - Malignancy

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  - Infections
  - Drug fever
  - Malignancy

EARLY EMPIRIC ANTIMICROBIAL THERAPY

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 if 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 test; e.g.

- HIV antibodies depending on detailed 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
- etc.

D Knockaert J Int med 2003;253:263

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-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; 350: 575-580.

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:

'common = common'

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

Petersdorf RT, Beeson PB. Fever of unexplained origin: Report on 100 cases.
Medicine 1961;40:1-30.

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

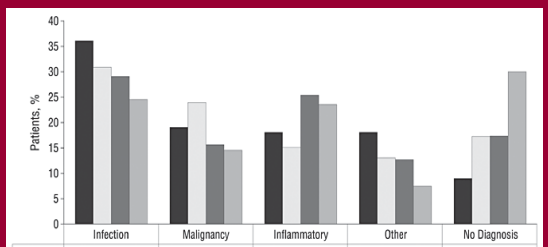
Vanderschueren S. et al. From prolonged febrile illness to Fever of Unknown Origin: The challenge continues. Arch Intern Med 2003;163:1033.

Diagnostic spectrum

Depends on:

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

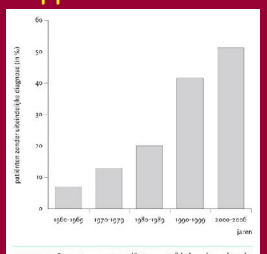
Time matters: the spectrum evolves



	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

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

Are we losing it? Apparent loss of diagnostic yield



FIGUUR 1. Percentages van patiënten met febris ecl zonder uiteindelijke diagnose, weergegeven per decennium tussen 1960 en 2007: 1960-1969;[1] 1970-1979;[10] 1980-1989;[7 11 12] 1990-1999;[5 9] 2000-2006.[3] De toename van het percentage is deels te verklaren door verandering van de definitie van febris ecl (uitsluiten van immuungecompromitteerde patiënten en meetellen van poliklinische patiënten), deels door verbeterde diagnostische technieken (de diagnose wordt vaker binnen 3 weken gesteld) en mogelijk door een meer afwachtende houding sinds bekend werd dat de prognose van patiënten met febris ecl zonder diagnose meestal goed is.

C.P. Bleeker-Rovers and J.W.M. van der Meer Ned Tijdschr Geneeskd. 2008;152:869-73.

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

Age matters

	Elderly (n = 204)	Young (n = 152)
Infection	**72 (35)**	**33 (22)**
- Tuberculosis	20 (10)	4 (3)
- Abscess	25 (12)	6 (4)
- Endocarditis	14 (7)	2 (1)
- Viral infections	1 (0.5)	8 (5)
Malignancies	**38 (19)**	**8 (5)**
NIID	**57 (28)**	**27 (17)**
Miscellaneous	**17 (8)**	**39 (26)**
No diagnosis	**18 (9)**	**45 (29)**

Norman D. Clin Inf Dis 2000;31:148

Periodicity of fever matters: Episodic versus continuous FUO

	recurrent fever n=45 (%)	continuous fever n=154 (%)	
infection	4 (8.8)	41 (26.6)	p< 0.025
tumour	2 (4.4)	12 (7.7)	NS
multisystem disease	4 (8.8)	38 (23.9)	p< 0.01
drug-related fever	1 (2.2)	5 (3.2)	NS
factitious fever	1 (2.2)	6 (3.8)	NS
habitual hyperthermia	0	5 (3.2)	NS
miscellaneous	10*(22.0)	19 (12.9)	NS
no diagnosis	23 (51.0)	28 (18.1)	p< 0.001

* Chron's disease (3) familial mediterranean fever (2), extrinsic allergic alveolitis, ankylosing spondylitis, Castleman's disease, inflammatory pseudotumor of lymph nodes, cholesterol embolism

Knockaert et al. Medicine 1993,72,184.

APPROACH TO THE ADULT WITH CLASSIC FUO

Initial approach

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

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to qualify as FUO

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D Knockaert J Int med 2003;253:263

Causes of FUO: big & little 3

- Infections
- Malignancies
- NIID's

Big three

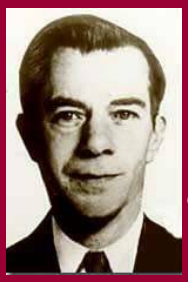
- Drug fever
- Factituous fever
- 'Habitual hyperthermia'

Little three

Rule out the little 3

- Rule out factituous fever: document the fever.
- Rule out habitual hyperthermia : temperature chart & settings
- Rule out drug fever: stop all nonessential medications

SUTTON'S LAW



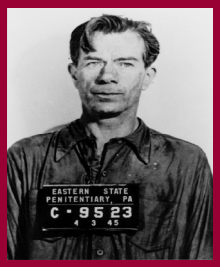
"Look where the money is!"

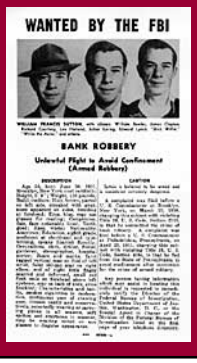
$$$$

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

Willie Sutton °1901- †1980

SUTTON'S LAW



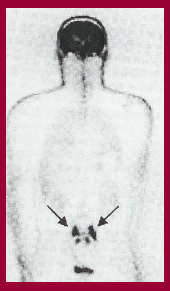


What if 'potentially diagnostic clues' are absent or prove to be misleading?

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

'WHOLE BODY INFLAMMATION TRACER SCINTIGRAPHY'

FDG-PET scintigrafy:
Large vessel vasculitis



FDG-PET scintigrafy:
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 trails are seldom diagnostically rewarding and tend to obscure rather than to illuminate.
- Symptomatic: NSAID
- Therapeutic trail to be considered in case of detorioration
  * 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

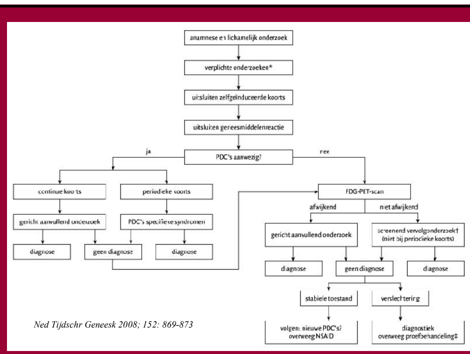
    Larson et al. Medicine 1982;61:269
- Hematological malignancies: 12% of diagnoses ≈ 60% of deaths

  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)

Knockaert et al. Arch Int Med 1996;156:618



anamnese en lichamelijk onderzoek
verplichte onderzoeken*
uitsluiten zelfgeïnduceerde koorts
uitsluiten geneesmiddelenreactie
ja
PDC's aanwezig?
nee
continue koorts
periodieke koorts
gericht aanvullend onderzoek
PDC's specifieke syndromen
diagnose
geen diagnose
diagnose
FDG-PET-scan
afwijkend
niet afwijkend
gericht aanvullend onderzoek
screenend vervolgonderzoek† (niet bij periodieke koorts)
diagnose
geen diagnose
diagnose
stabiele toestand
verslechtering
volgen: nieuwe PDC's? overweeg NSAID
diagnostiek overweeg proefbehandeling‡
Ned Tijdschr Geneesk 2008; 152: 869-873

FIGUUR 2. Diagnostisch algoritme bij febris eci; (*) bepaling van: BSE, C-reactief proteïne, Hb, trombocyten, leukocyten met differentiatie, natrium, kalium, creatinine, totaaleiwit, eiwit-elektroforese, alkalische fosfatase, aspartaataminotransferase (ASAT), alanineaminotransferase (ALAT), lactaatdehydrogenase, creatinekinase, antinucleaire antistoffen, reumafactor, urinesediment; uitvoering van bloedkweek (3 maal), urinekweek, thoraxröntgenfoto, echografie van het abdomen en mantouxtest; (†) vervolgonderzoek: fundoscopie, CT van thorax en abdomen, beenmergbiopsie en bij patiënten ouder dan 55 jaar A.-temporalisbiopsie; (‡) proefbehandeling: antibiotica, tuberculostatica, corticosteroïden. PDC = potentieel diagnostische 'clues': alle lokaliserende klachten, symptomen en afwijkingen in het aanvullend onderzoek die in de richting wijzen van een bepaalde diagnose (voorbeeld: lymfadenopathie bij een uiteindelijke diagnose van de ziekte van Hodgkin); FDG-PET = ^{18}F-fluorodeoxyglucose-positronemissietomografie.

"… 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.

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'.