PYREXIA OF UNKNOWN ORIGIN

Fever of unknown origin (FUO) was defined by Petersdorf and Beeson in 1961 as

- (1) temperatures of >38.3°C (>101°F) on several occasions;
- (2) a duration of fever of >3 weeks; and
- (3) failure to reach a diagnosis despite 1 week of inpatient investigation.

Durack and Street have proposed a new system for classification of FUO:

- (1) classic FUO;
- (2) nosocomial FUO;
- (3) neutropenic FUO; and
- (4) FUO associated with HIV infection.

Classic FUO

- differing only with regard to the prior requirement for 1 week's study in the hospital.
- three outpatient visits or 3 days in the hospital without elucidation of a cause or 1 week of "intelligent and invasive" ambulatory investigation.

NOSOCOMIAL FUO

- temperature of 38.3°C (101°F) develops on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest or incubating on admission.
- Three days of investigation, including at least 2 days' incubation of cultures, is the minimum requirement for this diagnosis.

Neutropenic FUO

- is defined as a temperature of 38.3°C (101°F) on several occasions in a patient whose neutrophil count is <500/L or is expected to fall to that level in 1–2 days.
- the diagnosis of neutropenic FUO is invoked if a specific cause is not identified after 3 days of investigation, including at least 2 days' incubation of cultures.

HIV-associated FUO

- is defined by a temperature of 38.3°C (101°F) on several occasions over a period of >4 weeks for outpatients or >3 days for hospitalized patients with HIV infection.
- This diagnosis is invoked if appropriate investigation over 3 days, including 2 days' incubation of cultures, reveals no source.

Table 19-1 Classic FUO in Adults

Authors (Year of Publication)	Years of Study	No. of Cases	Infections (%)	Neoplasms (%)	Noninfectious Inflammatory Diseases (%)	Miscellaneous Causes (%)	Undiagnosed Causes (%)
Petersdorf and Beeson (1961)	1952–1957	100	36	19	19*	19*	7
Larson and Featherstone (1982)	1970–1980	105	30	31	16*	11a	12
Knockaert and Vanneste (1992)	1980–1989	199	22.5	7	23*	21.5*	25.5
de Kleijn et al. (1997, Part 1)	1992–1994	167	26	12.5	24	8	30

*Authors' raw data retabulated to conform to altered diagnostic categories.

Table 19-2 Causes of FUO Lasting >6 Months

Cause	Cases, %
None identified	19
Miscellaneous causes	13
Factitious causes	9
Granulomatous hepatitis	8
Neoplasm	7
Still's disease	6
Infection	6
Collagen vascular disease	4
Familial Mediterranean fever	3
No fever*	27

*No actual fever observed during 2–3 weeks of inpatient observation. Includes patients with exaggerated circadian rhythm.

ETIOLOGY

Three general categories of illness account for the majority of "classic" FUO cases and have been consistent through the decades.

These categories are:

- • Infections
- • Malignancies
- • Connective tissue diseases (eg, vasculitis, rheumatoid arthritis).

Common causes of FUO

- Connective tissue disease-22%
- Infection -16%(TB and Abscess)
- Malignancy-7%
- Miscellaneous-4%
- No diagnosis-51%

The most common malignancies to present with FUO are:

- • Lymphoma, especially non-Hodgkin's
- • Leukemia
- • Renal cell carcinoma
- • Hepatocellular carcinoma or other tumors metastatic to the liver

Most common rheumatologic disorders presenting as FUO

- Adult Still's disease in young and middle-aged adults
- Giant cell arteritis (GCA) in older individuals
- GCA accounts for approximately 15 percent of cases of FUO in the elderly.

Drugs

- cause fever by stimulating an allergic or idiosyncratic reaction, or by affecting thermoregulation.
- One-third of hospitalized patients suffer from adverse drug reactions, including "drug fever."
- Eosinophilia and rash accompany drug fever in only 25 percent of cases; thus, the absence of these findings should not preclude a search for a possible offending drug .

The most common drugs that cause fever include:

- Antimicrobials (sulfonamides, penicillins, nitrofurantoin, vancomycin, antimalarials)
- H1 and H2 blocking antihistamines
- Antiepileptic drugs (barbiturates and phenytoin)
- Iodides
- Nonsteroidal antiinflammatory drugs (including salicylates)

- Antihypertensive drugs (hydralazine, methyldopa)
- Antiarrhythmic drugs (quinidine, procainamide)
- Antithyroid drugs
- Contaminants such as quinine that accompany injected cocaine or heroin
- A number of drugs rarely cause fever, such as digoxin and aminoglycosides.

LESS COMMON CAUSES

Infections	Malignancies	Systemic diseases	Miscellaneous
Amebic liver abscess	Atrial myxoma	Allergic granulomatous angiitis	Behcet's disease
Brucellosis	Aleukemic leukemia	Antiphospholipid syndrome	Chronic fatigue syndrome
Chronic active hepatitis	Colon carcinoma	Granulomatous hepatitis	Disorders of temperature regulation (neurologic and dermatologic)
Cytomegalovirus	Kaposi's sarcoma	Hypersensitivity vasculitis	Drug fever
Dental abscesses	Lung cancer	Inflammatory bowel disease	Environmental (metal and polymer fume fevers)
Diskitis	Multiple myeloma	Panarteritis	Factitious fever
Epididymitis	Sarcoma	Reiters syndrome	Familial
Fascioliasis		Sarcoidosis	Mediterranean fever
Gonococcal arthritis			Neuroleptic malignant syndrome
Herpes simplex encephalitis			Periodic fever
Infectious mononucleosis			Pulmonary emboli
Kala azar			Retroperitoneal hematomas
Kikuchi's disease			Thyroiditis
Lyme disease			
Prostatitis			
Pyelonephritis			
Pyomyositis			
Rheumatic fever			
Sinusitis			
Typhoid fever			
Whipple's disease			

DIAGNOSTIC APPROACH

- Take a careful history and
- Reassess the patient frequently.
- It is important to look for uncommon presentations of common diseases
- Perform a detailed physical examination.

A thorough history should include the following information:

- Travel
- Animal exposure (eg, pets, occupational, living on a farm)
- Immunosuppression (with the degree noted)
- Drug and toxin history, including antimicrobials
- Localizing symptoms

Subtle findings may be elicited through a careful history.

- subtle changes in behavior or cognition consistent with granulomatous meningitis;
- jaw claudication consistent with giant cell arteritis;
- and nocturia consistent with prostatitis.

Diagnostic testing

- Erythrocyte sedimentation rate or C-reactive protein
- Serum lactate dehydrogenase
- Tuberculin skin test
- HIV antibody assay and HIV viral load for patients at high risk
- Three routine blood cultures drawn from different sites over a period of at least several hours without administering antibiotics, if not already performed

- Rheumatoid factor
- Creatine phosphokinase
- Heterophile antibody test in children and young adults
- Antinuclear antibodies
- Serum protein electrophoresis
- CT scan of abdomen
- CT scan of chest

Therapeutic trials

Therapeutic trials of antimicrobials or glucocorticoids, while tempting in the effort to "do something," rarely establish a diagnosis.

In addition, the diagnostic yield of blood cultures and cultures of biopsy material will be reduced following the initiation of antibiotics.

Antimicrobial agents could be expected to suppress, but not cure, an infectious process such as an occult abscess since adjunctive drainage would usually be required.

Therapeutic trials

- Antibiotics can have effects on other infections than the ones to which therapy is directed.
- Rifampin, for example, used in a therapeutic trial for tuberculosis may suppress staphylococcal osteomyelitis or diminish the ability to detect difficult to isolate organisms causing endocarditis.
- The appropriate duration of a therapeutic trial is also unclear since a number of infections such as endocarditis or pelvic inflammatory disease can take as much as one week for fever to abate, even with appropriate therapy.
- Thus, patients with FUO should not have empiric antibiotics started solely to treat fever.

Therapeutic trials

- A therapeutic trial of glucocorticoids for an inflammatory process should not replace relevant biopsies for steroid-responsive disease such as sarcoidosis, other granulomatous diseases, or vasculitis.
- A careful evaluation for infection should precede such a trial.
- No diagnosis — The rate of no diagnosis in studies of FUO published since 1990 has varied widely from 9 to 51 percent.

OUTCOME

- The outcome of patients with an FUO depends upon the underlying diagnosis.
- Among children with FUO, 88 percent of those caused by infections have no sequelae.
- Most adults who remain undiagnosed after an extensive evaluation also have a good prognosis .

OUTCOME

This was illustrated in a study of 199 patients with FUO, 61 of whom (30 percent) were discharged from the hospital without a diagnosis :-

- A definite diagnosis was established in 12, usually within two months after discharge.
- Thirty-one became symptom-free during hospitalization or shortly following discharge.
- Eighteen had persisting or recurring fever for several months or even years after discharge, 10 of whom were considered to be finally cured.
- Four were treated with glucocorticoids and six required intermittent therapy with nonsteroidal antiinflammatory drugs.
- Six died, but the cause of death was considered to be related to the disease that caused FUO in only two cases.

SUMMARY AND RECOMMENDATIONS

- Fever of unknown origin (FUO) is defined as fever higher than 38.3ºC on several occasions lasting for at least three (some use two) weeks without an established etiology despite intensive evaluation and diagnostic testing.
- Three general categories of illness account for the majority of "classic" FUO cases and have been consistent through the decades. These categories are infections, malignancies, and connective tissue diseases.
- The incidence of specific etiologic agents of FUO varies by age of the population, by potential exposure to infectious agents, by host susceptibility to infection, and over time with advances in diagnostics in identifying the etiologic agent.

- The most important aspects of the evaluation of a patient with FUO are to take a careful history, perform a detailed physical examination, and to reassess the patient frequently.
- Should recommend the following minimum diagnostic evaluation: blood cultures, erythrocyte sedimentation rate or C-reactive protein, serum lactate dehydrogenase, HIV antibody test and viral load, rheumatoid factor, heterophile antibody test, creatine phosphokinase, antinuclear antibodies, tuberculin skin test, serum protein electrophoresis, and CT scan of abdomen and chest. (
- The primary evaluation and diagnostic workup can suggest a directed biopsy that may establish the diagnosis.
- The diagnostic evaluation may fail to identify an etiology in as many as 30 to 50 percent of patients. Most adults who remain undiagnosed have a good prognosis.