Fever of Unknown Origin

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FUO

- Most episodes of fever in humans are
  - short-lived
  - do not require diagnostic investigation or specific therapy.
- Some episodes of fever in humans
  - can be readily diagnosed and
  - effectively treated
- However, a small but important subgroups of fever are
  - persistent and
  - difficult to diagnose.

FUO

- Such puzzling fevers have fascinated and frustrated clinicians since the earliest days of clinical studies
  - *Prolonged and Perplexing Fevers, published by Keefer and* Leard in 1955
  - *Fever of Unknown Origin: Report on 100 cases, by* Petersdorf and Beeson in 1961

Terminology and Definition

- In the United States, The term
  - *fever of unknown origin (FUO) is generally* used.
- In other countries an alternative term,
  - *pyrexia of unknown origin (PUO), is often used.*

Terminology and Definition

- The first formal definition of FUO by Petersdorf and Beeson nearly five decades ago:
  - fever higher than 38.3° C
  - persisting without diagnosis for at least 3 weeks
  - persisting at least 1 week's investigation in hospital

Terminology and Definition

- Investigators have modified and extended this classical definition
  - Classical FUO
  - Health Care Associated FUO
  - Immune-deficient FUO
  - HIV-related FUO
- Computed axial tomography, magnetic resonance imaging, ultrasound imaging, nucleic acid–based diagnostic testing, and rapid tests for pathogens have changed the landscape of FUO.

Four Subtypes of FUO

	Classical FUO	*Health care–associated FUO*	*Immune-Deficient FUO*	*HIV-Related FUO*
Definition	>38.0° C, >3 wk, >2 visits or 3 days in hospital	>38.0° C, >3 days, not present or incubating on admission	>38.0° C, >3 days, negative cultures after 48 hr	38.0° C, >3 wk for outpatients, >3 days for inpatients, HIV infection confirmed
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed habitual hyperthermia	Health care–associated infections, postoperative complications, drug fever	Majority due to infections, but cause documented in only 40%-60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)

Classical fever of unknown origine

- Most patients with classical FUO have subacute or chronic symptoms and therefore can be safely investigated as outpatients.

- In a series of 53 FUO patients; the median duration of fever before diagnosis was 40 days.

Classical fever of unknown origine

- Disorders causing classical FUO in five categories:
  - Infections
  - Neoplasms
  - Connective tissue diseases
  - Miscellaneous other disorders
  - Undiagnosed illnesses

Classical fever of unknown origine

- In most series, infections are the largest category,
  - accounting for 25% to 50% of cases
- However, if patients older than 65 years,
  - infections become less common,
  - falling into second or third place as a cause of classical FUO

Classical fever of unknown origine

- Among the infections responsible for classical FUO :
  - abscesses
  - endocarditis
  - tuberculosis
  - complicated urinary tract infections
    - have consistently been among the most important.
- Infections tend to vary in incidence according to locale.
  - Visceral leishmaniasis, 8% of cases reported from Spain.
  - Familial Mediterranean fever in Ashkenazi Jews
  - Kikuchi's disease (an unusual form of necrotizing lymphadenitis) primarily in Japan
  - TRAPS (TNF-receptor associated periodic fever), formerly called familial Hibernian fever in Ireland

Classical fever of unknown origine

- The miscellaneous category rare causes of classical FUO:
  - Addison's disease
  - Adult Still's disease
  - Alcoholic hepatitis
  - Aortic dissection
  - Behçet's syndrome
  - Chronic meningitis
  - Erythema multiforme
  - Fabry's disease
  - Granulomatous hepatitis
  - Histiocytosis X
  - Inflammatory bowel disease
  - Pheochromocytoma
  - Sarcoidiosis
  - Vitamin B12 deficiency and more specific diseases

Classical fever of unknown origine

Allergic alveolitis
Atrial myxoma
Autoimmune cholangitis
Bartonellosis
Carcinomatous meningitis
Castleman's disease
Cirrhotic fever
Cyclic neutropenia
Drug fever and other Hypersensitivities
Factitious fever
Familial Hibernian fever
Familial Mediterranean fever
Giant coronary aneurysm
Granulomatous peritonitis
Hantavirus infection
Hemoglobinopathies
Hemolytic anemias
Hemophagocytic syndrome
Human picornavirus infection

Hypereosinophilic syndrome
Immunoblastic lymphadenopathy
Infected urachal cyst
Kikuchi-Fujimoto disease
Lofgren syndrome
Lymphomatoid granulomatosis
Metal fume fever
Myeloproliferative syndromes
Pancreatitis
Parathyroid apoplexy
Paroxysmal hemoglobinurias
Pericarditis
Periodic fever
Polyarteritis nodosa
Postpericardiotomy syndrome
Pulmonary emboli
Resorbing hematoma
Retroperitoneal fibrosis
Rosai-Dorfman disease
Schnitzler's syndrome
Sinusitis
Serum sickness
Sjögren's syndrome
Subacute necrotizing lymphadenitis
Thrombotic thrombocytopenic purpura
Thyroiditis and thyrotoxicosis
Veno-occlusive disease
Wegener's granulomatosis
Whipple's disease

Classical fever of unknown origine

- Connective tissue diseases responsible for classical FUO,
  - Still's disease (juvenile rheumatoid arthritis)
  - other variants of rheumatoid arthritis
  - systemic lupus erythematosus
    - predominate in younger patients,
- Whereas
  - temporal arteritis
  - polymyalgia rheumatica syndromes
    - are more common in elderly patients.

Classical fever of unknown origine

- Malignant neoplasms,
  - can induce fever directly through the production and release of pyrogenic cytokines (lymphomas)
  - They can also generate fevers indirectly by undergoing spontaneous or induced necrosis or by creating conditions to secondary infections,
    - such as postobstructive pneumonia

Classical fever of unknown origine

- Infants and children :
- The diseases responsible for classical FUO in infants differ from those in older children and adults.
- Respiratory infections cause classical FUO in infants more often than in children older than 12 months or in adults.
- The relative frequency of infections as the cause of FUO in infants is high, connective tissue diseases and cancers are rare in this age group.

Classical fever of unknown origine

- Kawasaki disease occurs in children younger than 5 years.
- Connective tissue diseases are rarely seen in children younger than 12 months,
- Still's disease is a leading cause of FUO in older children and young adults.
- Joint involvement in children with FUO usually signifies a serious underlying disorder, such as
  - Connective tissue disease,
  - Endocarditis,
  - Leukemia.

Classical fever of unknown origine

- In a series of 146 pediatric cases of FUO, established a specific diagnosis in only 84(57.5%).
- Of these,
  - 64 (43.8%) Infections,
  - 11 (7.5%) Autoimmune disorders,
  - 4 (2.7%) Malignant neoplasms,
  - 5 (3.4%) a variety of other disorders, such as drug-induced fever, sarcoidosis, and mercury poisoning.

Classical fever of unknown origine

- The most common infectious diseases diagnosed in this series were
  - Epstein-Barr virus (EBV) infection (15%),
  - Osteomyelitis (10%),
  - Bartonellosis (5%),
  - Urinary tract infections (4%).

Classical fever of unknown origine

- Elderly person :
- Classical FUO in patients older than 65 years is the relatively high frequency with which connective tissue diseases are identified as the cause of the illness
- In developed countries, connective tissue diseases surpass even infections as the leading cause of classical FUO in the elderly
  - temporal arteritis
  - polymyalgia rheumatica syndromes

Classical fever of unknown origine

- In elderly patients infections are identified as the cause of FUO,
  - Intra-abdominal abscesses,
  - Complicated urinary tract infections,
  - Tuberculosis,
  - Endocarditis

Classical fever of unknown origine

DİAGNOSİS	< 65 YEARS n: 152	> 65 YEARS n:201
Infections	72 (%35)	33 (%21)
Tumors	8 (%5)	37 (%19)
Multisystem diseases	27 (%17)	57 (%28)
Miscellaneous	39 (%26)	17 (% 8)
No diagnosis	45 (%29)	18 (%9)

DİAGNOSİS	Mac Lean et al n:587	Doherty et al n:195
Malaria	32	42
Hepatitis	6	3
Respiratory infections	11	2.6
UTİ / Pyelonephritis	4	2.6
Dysentry	4.5	5.1
Dengue fever	2	6.2
Enteric fever	2	1.5
Tuberculosis	1	2
Rickettsial infections	1	0.5
Acute HIV infection	0.3	1
Amebic liver abscess	1	0
Other miscallenous infections	4.3	9.2
Miscallenous noninfectious diseases	6	1
UNDİAGNOSED	25	24.6

Classical fever of unknown origine

- Fever in returned travelers is most often due to common infections, such as
  - Malaria
  - Respiratory tract Infections
  - Urinary tract infections

Health Care-Associated FUO

- *Health care–associated FUO is a condition in* which patients first manifest fever during active medical treatment for some other illness.
- Such FUO cases are frequently attributable to risk factors encountered in the health care environment,
  - Surgical procedures
  - Urinary and Respiratory tract instrumentation
  - Intravascular devices
  - Drug therapy
  - Immobilization

Immune-Deficient FUO

- Various forms of immunosuppression predispose more or less strongly to a wide variety of infectious complications.

- Thus, immunosuppressed patients have perhaps the highest incidence of FUO of any group of patients.

Immune-Deficient FUO

- In patients with impaired cell-mediated immunity, FUO is often due to :
  - Infections % 58
  - Non-infectious %25
  - Undetermined % 17

Immune-Deficient FUO

- Neutropenic FUO :
- Neutropenia is a dangerous condition that can be considered a special subclass of immunodeficiency.
- The number of patients with episodes of neutropenia resulting from
  - Cytotoxic therapy
  - Malignancies affecting the bone marrow

Immune-Deficient FUO

- Episodes of fever are common in patients with neutropenia.

- Many such episodes are short-lived, because
  - either respond quickly to treatment
  - or rapidly fatal infections.

Immune-Deficient FUO

- Bacteremia and sepsis are frequent causes, empirical broad-spectrum antibiotics should be administered promptly, without waiting for the results of cultures, when fever develops in neutropenic patients.
- However, only about 35% of prolonged episodes of febrile neutropenia respond to broad-spectrum antibiotic therapy.

Immune-Deficient FUO

- If fever does not respond promptly to antibacterial therapy, fungal infection must be responsible, other causes are equally likely to be identified
  - Resistant bacterial infections
  - Tuberculosis, Toxoplasma gondii
  - Greft-Versus-Host disease
  - Drug fever
  - Toxic effect of chemotherapy

HIV- Related FUO

- The primary phase of HIV **infection is characterized by a mononucleosis-like illness in which fever is a prominent feature.**

- Once symptoms of the primary phase of the HIV infection resolve, HIV-infected patients enter a long period of subclinical infection during which they are usually afebrile

HIV- Related FUO

- However, in the later phases of untreated HIV infection,
  - episodes of fever become common,
  - often signifying a superimposed illness.

- Many of these are potentially devastating opportunistic infections

Clinical Evaluation of FUO

- The evaluation of a patient with FUO typically includes :
  - comprehensive history,
  - verification that the patient actually has fever,
  - consideration of the fever pattern,
  - repeated physical examinations, every day
  - laboratory investigations,
  - imaging studies,
  - invasive diagnostic procedures

Clinical Evaluation of FUO/ History

- History is a cornerstone of the evaluation of FUO.
- The history can be especially important in determining the choice of the initial laboratory investigations.
- Particular attention should be given to :
  - recent travel,
  - exposure to pets and other animals,
  - the work environment,
  - recent contact with people exhibiting similar symptoms.
  - family history (FMF)
  - past medical history (lymphoma, rheumatic fever, intra-abdominal disorders)
  - obtained medications

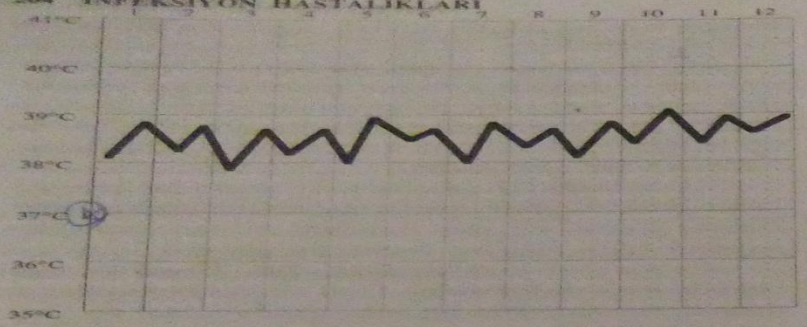
Clinical Evaluation of FUO/ Fever

- Next step is to verify the presence of fever.

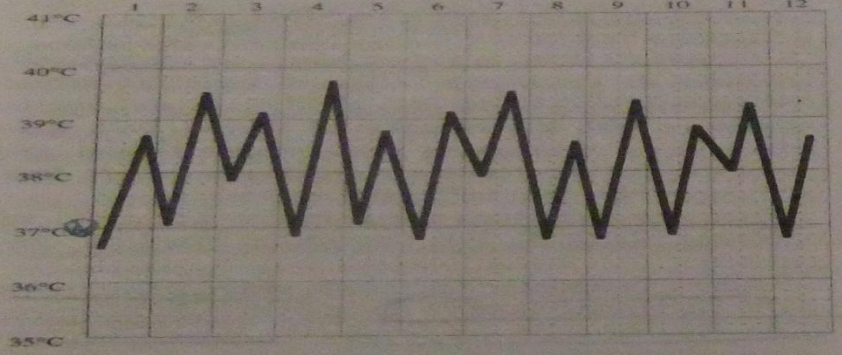
- In fact, in a series of 347 patients admitted to the National Institutes of Health for investigation of prolonged fever, 35% were ultimately determined either not to have significant fever at all, or to have fever of factitious origin.

Clinical Evaluation of FUO/ Fever

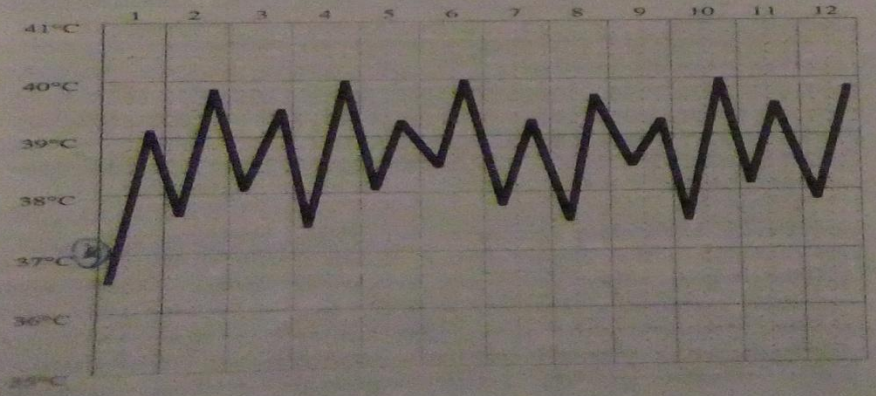
- *Febris continue*
- *Febris recurrens*
- *Intermittent (Hectic)*
- *Febris undulens (Pel - Ebstein)*
- *Remittent*
- *Subfebril fever*



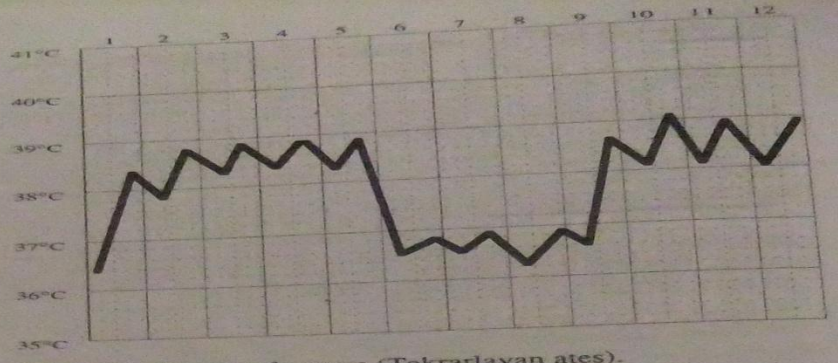
Şekil 21.1.4: Febris continue (Devamlı ateş)



Şekil 21.1.5: Febris intermittent (Aralıklı ateş).

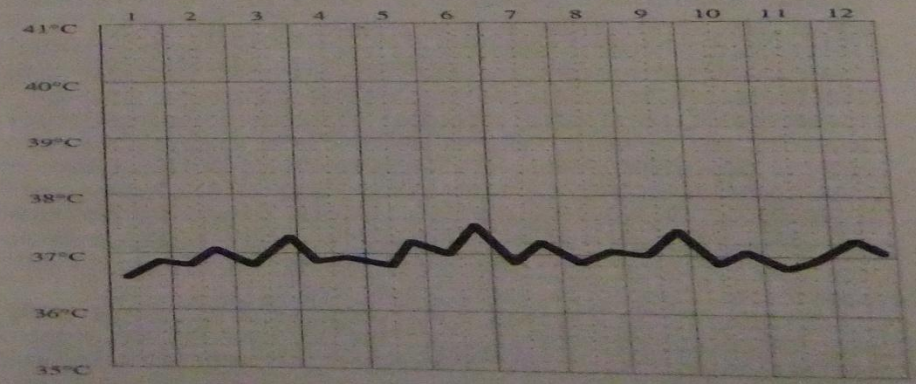


Şekil 21.1.6: Febris remittent (Bacaklı ateş) .



Şekil 21.1.7: Febris rekurrens (Tekrarlayan ateş).

Şekil 21.1.8: Febris undulens (Ondülan ateş).



Şekil 21.1.9: Subfebril ateş.

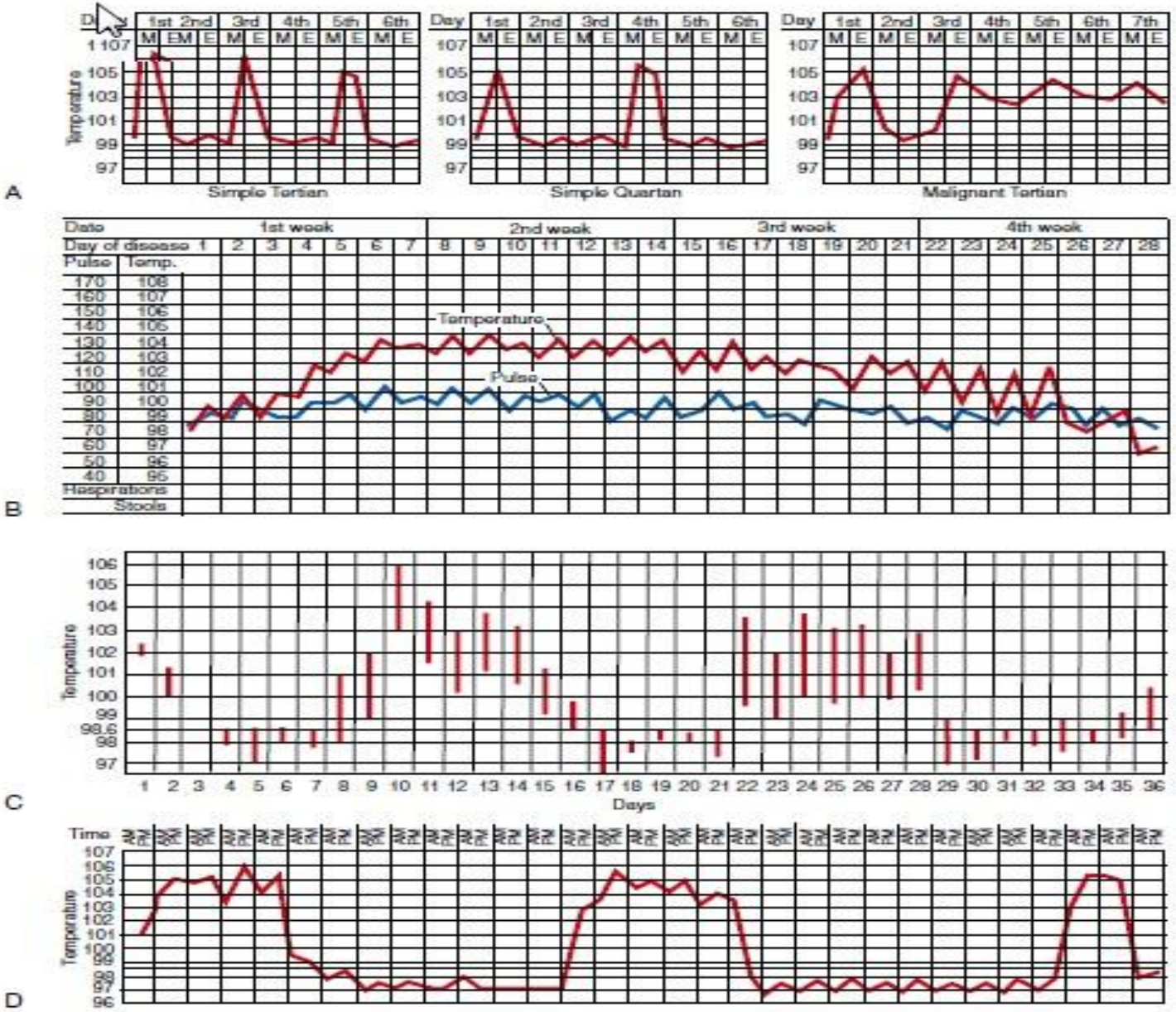


Figure 51-2 **Distinctive fever patterns. A,** Malaria. **B,** Typhoid fever (demonstrating relative bradycardia). **C,** Hodgkin's disease (Pel-Ebstein pattern). **D,** Borreliosis (relapsing fever pattern). *(From Woodward TE. The fever pattern as a clinical diagnostic aid. In: Mackowiak PA, ed. Fever. Basic Mechanisms and Management. 2nd ed. Philadelphia: Lippincott-Raven; 1997:215-236.)*

Clinical Evaluation of FUO/ Fever

- Pulse-temperature disassociation sometimes seen in typhoid fever, atypic pneumoniae
- 1 degree elevated fever, resulted with elevated 20 heart beats

Clinical Evaluation of FUO/ physical examination

- Frequently, key physical abnormalities in patients with FUO are so subtle as to require repeated examinations to be appreciated.
- Examples
  - include the nodular or weakly pulsatile temporal artery of
    - temporal arteritis,
  - oral ulcers of
    - disseminated histoplasmosis or Behçet's syndrome,
  - choroid granuloma or epididymal nodule of
    - extrapulmonary tuberculosis,
  - the testicular nodule of
    - polyarteritis nodosa,
  - Rectal fluctuance of a
    - perirectal abscess.

Clinical Evaluation of FUO/ physical

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
HEAD	Sinus tenderness	Sinusitis
TEMPORAL ARTERY	Nodules,reduced pulsation	Temporal arteritis
OROPHARYNX	Ulceration Tender tooth	Histoplasmotosis Periapical abscees
FUNDUS CONJUNCTİVA	Choroid Tubercule Petechiaei,Roth spot's	Dissemine granulomatosis Endocarditis
THYROİD	Enlargment,tenderness	Thyroiditis
HEART	Murmur	Infective endocarditis
ABDOMEN	LAP, Splenomegaly	Lymphoma,endocarditis, Dissemine granulomatosis
RECTUM	Perirectal fluctuance	Abscess
GENİTALİA	Testicular nodule Epididymal nodule	Periarteritis nodosa Dissemine granulomatosis
LOWER EXTREMİTİES	Deep venous tenderness	Thrombosis,thromboflebitis
SKİN AND NAİLS	Petechiae, clubbing, splinter hemorhages, subcutaneous nodule	Vasculitis, endocarditis

Clinical Evaluation of FUO/ Laboratory Investigations

- In most series, noninvasive laboratory tests have yielded the diagnosis in approximately a quarter of the cases.
- The most useful of these
  - serologic tests
  - blood smears
  - microbial culture

Clinical Evaluation of FUO/ Laboratory Investigations

- Bone marrow examination should be considered for diagnosis of suspected granulomatous diseases
  - Tuberculosis,
  - Histoplasmosis,
  - Sarcoidosis,
  - Carcinomatosis
  - Hemophagocytic syndrome

Clinical Evaluation of FUO/ Laboratory Investigations

- Ultrasound imaging (USG)
- Computed tomography imaging(CT)
- Magnetic resonans imaging (MR)
- Scanning with labeled autologous leukocytes
- Gallium 67 scanning
- Positron emission tomography (PET)

Clinical Evaluation of FUO/Invasive Diagnostic Procedures

- Histopathologic examination of tissues obtained by
  - Excisional biopsy,
  - Needle biopsy,
  - Laparoscopy
  - Laparotomy,

- But in most published series of FUO patients, biopsy gave the final answer in less than half.

Clinical Evaluation of FUO/Invasive Diagnostic Procedures

- The diagnostic yield of operative and CT-guided biopsies is higher than that of old-style bedside biopsy procedures.
- For this reason, bedside biopsies should rarely be performed today

Clinical Evaluation of FUO/Invasive Diagnostic Procedures

- Exploratory laparotomy, once a prominent procedure in the workup of FUO, is rarely performed today, unless localized abdominal physical signs or imaging findings, or both, are present.
- This is because few abdominal anatomic abnormalities are currently missed by CT scanning or MRI,
  - vasculitis,
  - polyarteritis nodosa,
  - granulomatous disease,
  - chronic cholecystitis

Therapeutic Trials of FUO

- In the past, empirical therapy with anti-inflammatory agents, such as
  - corticosteroids,
  - aspirin,
  - antimicrobial agents,
  - In rare cases, even antineoplastic drugs were used for this purpose.

  - Today such trials are seldom indicated.

Therapeutic Trials of FUO

- The limitations and risks of empirical therapeutic trials are obvious.
- Underlying diseases may remit spontaneously during the course of ineffective therapy, giving the false impression of success.
- Furthermore, empirical treatment is rarely specific. Rifampin, for example, is likely to be included in empirical therapeutic regimens for tuberculosis, but is highly active against numerous bacterial species other than *Mycobacterium tuberculosis.*

Therapeutic Trials of FUO

- Similarly, fevers caused by malignant neoplasms have been reported to respond better to nonsteroidal anti-inflammatory agents such as naproxen than fevers of infectious origin,
- but the action of naproxen is nonspecific; the ability of the so-called naproxen test to differentiate malignant from nonmalignant causes of FUO remains unvalidated.

Therapeutic Trials of FUO

- For these reasons, therapeutic trials, even when successful in reducing fever, may delay the correct diagnosis and thus the appropriate treatment of FUO.

Management

- A fundamental principle in the management of classical FUO is that therapy should be withheld, whenever possible, until the cause of the fever has been determined, so that treatment can be tailored to a specific diagnosis.
- In febrile neutropenic patients, the principles of treatment are entirely different.
- Neutropenic patients should generally receive broad-spectrum antimicrobial therapy immediately after samples for appropriate cultures have been obtained

Prognosis

- Elderly patients with malignant neoplasms have the poorest prognosis.
- Diagnostic delay affects the prognosis adversely in
  - intra-abdominal infections,
  - miliary tuberculosis,
  - disseminated fungal infections,
  - recurrent pulmonary emboli

General diagnostic evaluation of patients with FUO

- Comprehensive history
- Repeated physical examinations
- Complete blood count
- Routine blood chemistry determinations
- Urinalysis, including microscopic examination
- Chest radiograph
- Erythrocyte sedimentation rate
- Antinuclear antibodies
- Rheumatoid factor
- Blood cultures: three or more separate specimens obtained in absence of antimicrobial therapy
- Cytomegalovirus IgM antibodies or viral detection in blood
- Heterophile antibody test in children and young adults
- Tuberculin skin test
- Computed tomography of abdomen, pelvis, or other sites
- Magnetic resonance imaging
- Radionuclide scans
- Human immunodeficiency virus antibodies or viral detection assay
- Further evaluation of any abnormality detected by above tests
- Venous duplex imaging of lower limbs