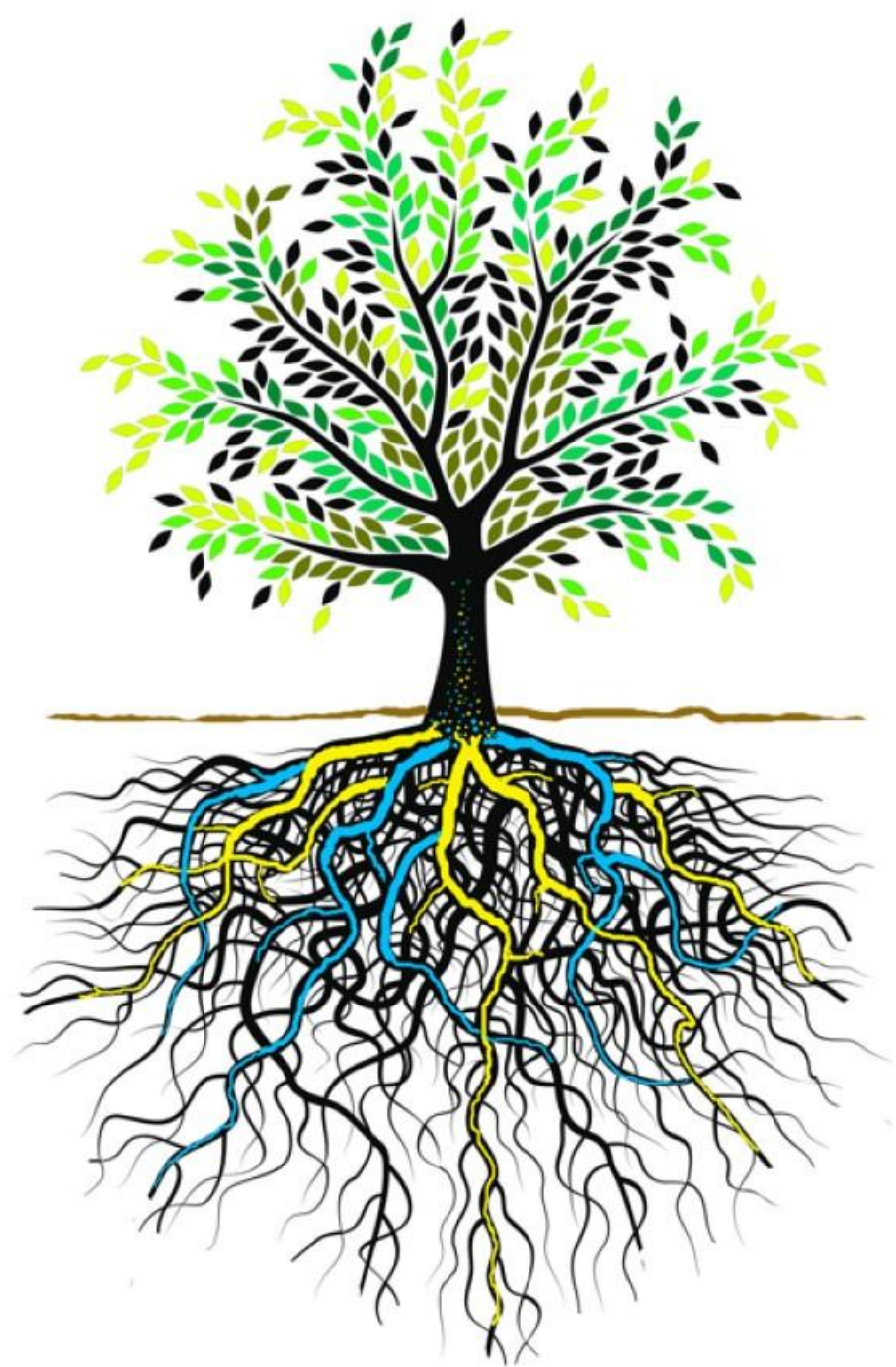


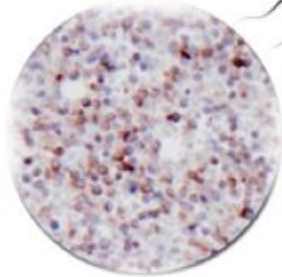
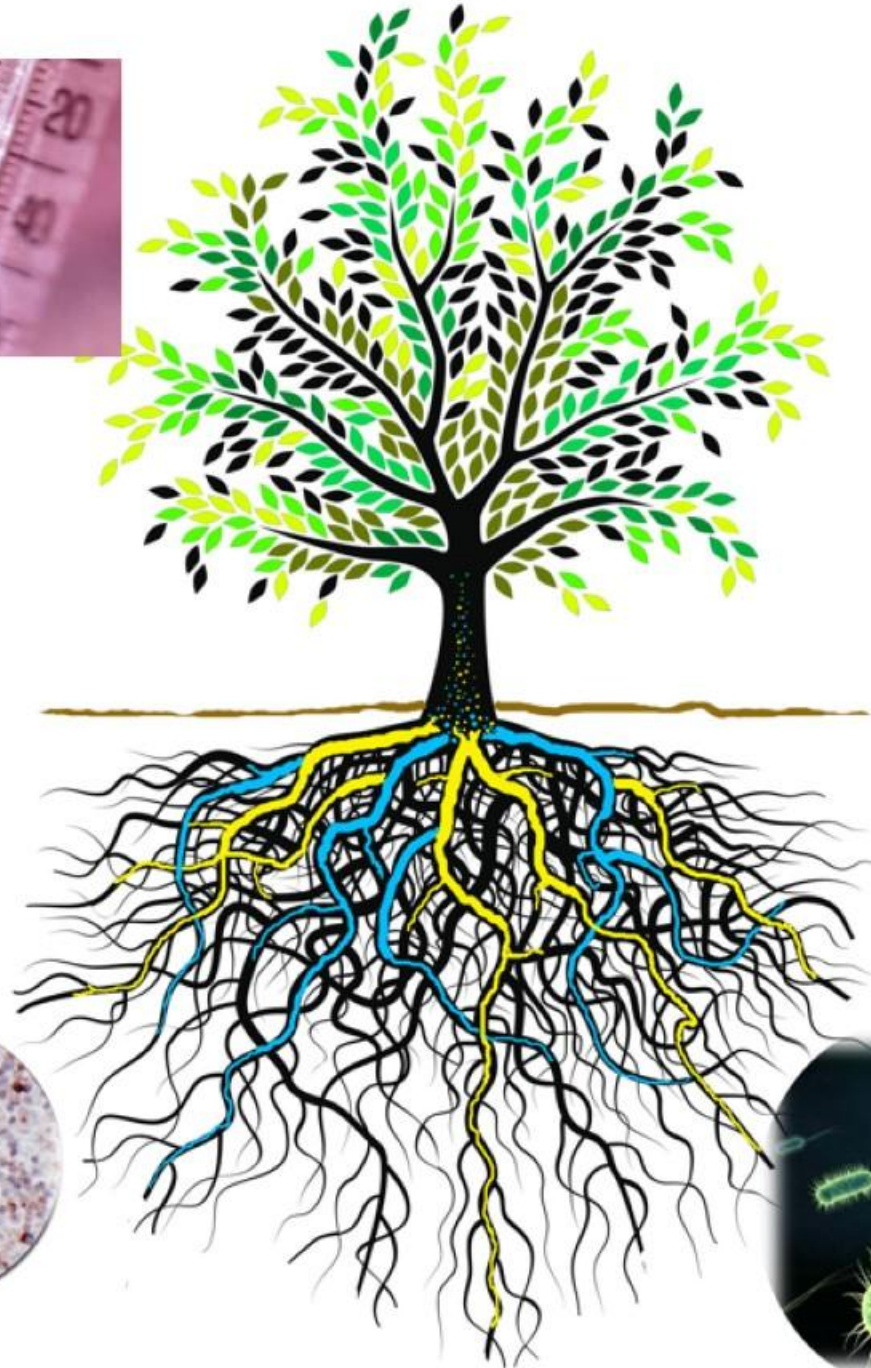
FEVER UNKNOWN ORIGIN (FUO)



Kovács Árpád Ferenc, University of Medicine and Pharmacy of Tîrgu Mureş

8th of March 2013





DEFINITION

Temperatures
of $>38.3^{\circ}\text{C}$ on
several
occasions

Duration of
fever of >3
weeks

Uncertain
diagnosis
after one
week in
hospital



CLASSIFICATION

classic

nosocomial

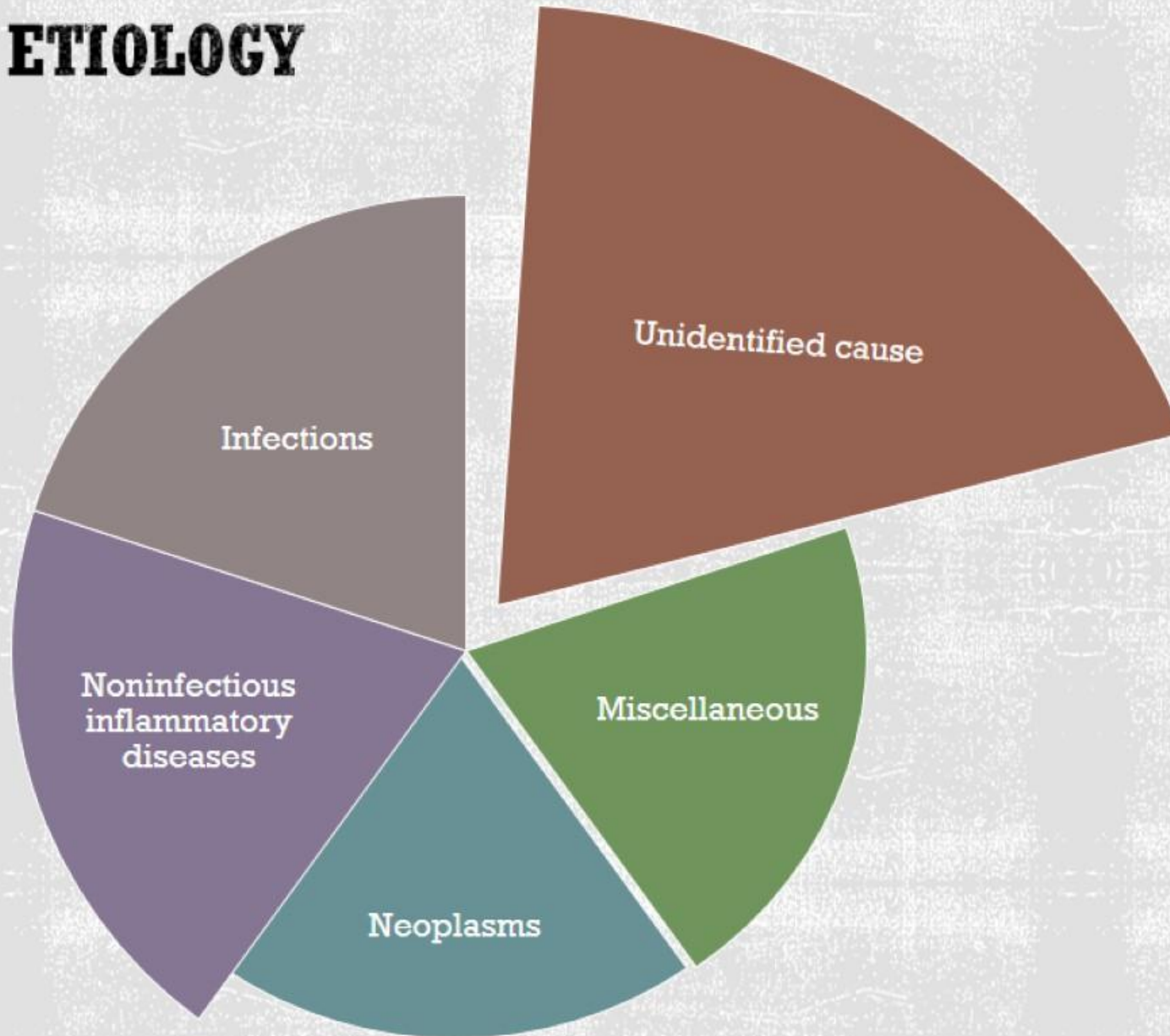
Neutropenic

neutrophil count is $<500/L$

associated
with HIV
infection



ETIOLOGY



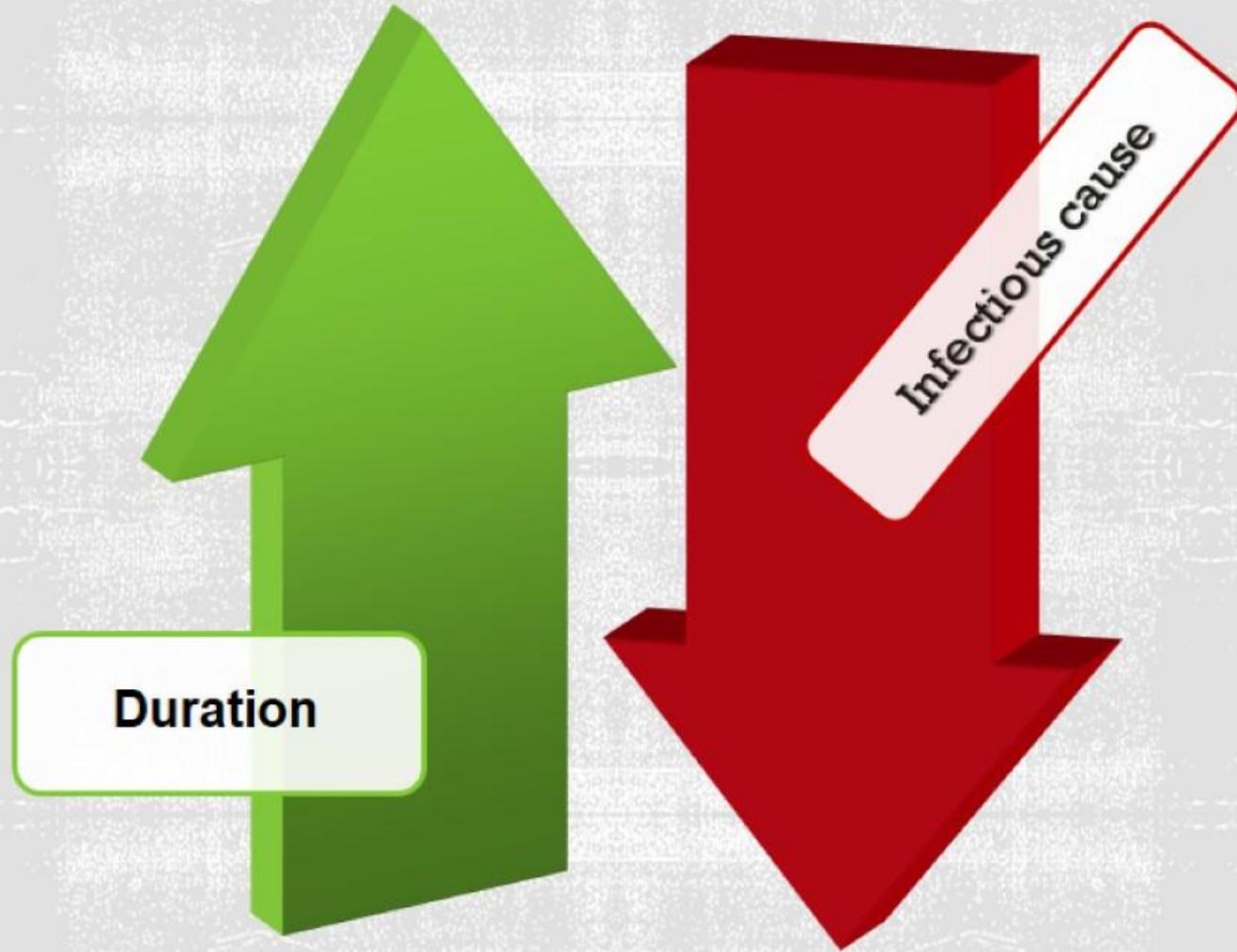
SYMPTOMS ASSOCIATED WITH FEVER

Symptoms	*Frequency (n=144)
Decreased appetite	69 (47.9%)
Vomiting	63 (43.7%)
Decreased activity	54 (37.5%)
General body ache/pain	52 (36.1%)
Headache	48 (33.3%)
Excessive cry	45 (31.2%)
Passage of loose stools	45 (31.2%)
Cough	45 (31.2%)
Runny nose	39 (27.1%)
Shivering	39 (27.1%)
Passage of yellow coloured urine	30 (20.8%)
Excessive sweating	30 (20.8%)
Yellowness of the eye	27 (18.7%)
Restlessness	27 (18.7%)
Fretfulness	27 (18.7%)
Abdominal pain	24 (16.7%)
Flushing of the face	21 (14.6%)
Skin rashes	15 (10.4%)
Constipation	15 (10.4%)
Shortage of blood	3 (2.1%)

* Frequency indicates multiple responses



TIMING



Timing is essential



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



CAUSES OF FUO IN ADULTS

Infections ≈36%

Localized pyogenic infections

Appendicitis

Cat-scratch disease

Cholangitis

Cholecystitis

Dental abscess

Diverticulitis/abscess

Lesser sac abscess

Liver abscess

Mesenteric lymphadenitis

Osteomyelitis

Pancreatic abscess

Pelvic inflammatory disease

Perinephric/intrarenal abscess

Prostatic abscess

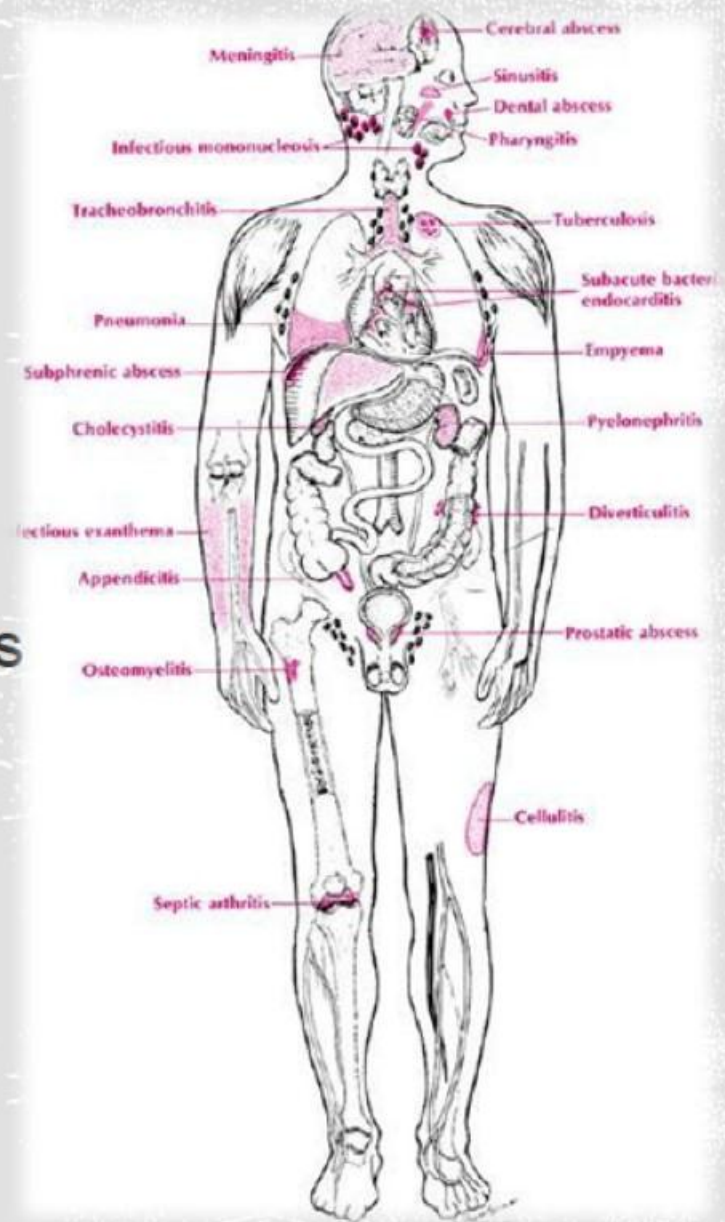
Renal malacoplakia

Sinusitis

Subphrenic abscess

Suppurative thrombophlebitis

Tuboovarian abscess



CAUSES OF FUO IN ADULTS

Infections 36%

Intravascular infections

Bacterial aortitis

Bacterial endocarditis

Vascular catheter infection

Systemic bacterial infections

Bartonellosis

Brucellosis

Campylobacter infection

Cat-scratch disease/bacillary angiomatosis (*B. henselae*)

Gonococchemia

Legionnaires' disease

Leptospirosis

Listeriosis

Lyme disease

Melioidosis

Meningococchemia

Rat-bite fever

Relapsing fever

Salmonellosis

Syphilis

Tularemia

Typhoid fever

Vibriosis

Yersinia infection



CAUSES OF FUO IN ADULTS

Infections

Mycobacterial infections

M. avium/M. intracellulare infections

Other atypical mycobacterial infections

Tuberculosis

Other bacterial infections

Actinomycosis

Bacillary angiomatosis

Nocardiosis

Whipple's disease

Rickettsial infections

Anaplasmosis

Ehrlichiosis

Murine typhus

Q fever

Rickettsialpox

Rocky Mountain spotted fever

Scrub typhus



CAUSES OF FUO IN ADULTS

Infections

Mycoplasmal infections

Chlamydial infections

Lymphogranuloma venereum

Psittacosis

TWAR (*C. pneumoniae*)
infection

Viral infections

Chikungunya fever

Colorado tick fever

Coxsackievirus group B
infection

Cytomegalovirus infection

Dengue

Epstein-Barr virus infection

Hepatitis A, B, C, D, and E

HIV infection

Human herpesvirus 6 infection

Lymphocytic choriomeningitis

Parvovirus B19 infection

Picornavirus infection



CAUSES OF FUO IN ADULTS

Infections

Fungal infections

Aspergillosis
Blastomycosis
Candidiasis
Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Mucormycosis
Paracoccidioidomycosis
Pneumocystis infection
Sporotrichosis

Parasitic infections

Amebiasis
Babesiosis
Chagas' disease
Leishmaniasis
Malaria
Strongyloidiasis
Toxocariasis
Toxoplasmosis
Trichinellosis
Presumed infections, agent undetermined
Kawasaki's disease (mucocutaneous lymph node syndrome)
Kikuchi's necrotizing lymphadenitis



CAUSES OF FUO IN ADULTS

Neoplasms \approx 15 %*

Malignant

Colon cancer

Gall bladder carcinoma

Hepatoma

Hodgkin's lymphoma

Immunoblastic T-cell lymphoma

Leukemia

Lymphomatoid granulomatosis

Malignant histiocytosis

Non-Hodgkin's lymphoma

Pancreatic cancer

Renal cell carcinoma

Sarcoma

Benign

Atrial myxoma

Castleman's disease

Renal angiomyolipoma



CAUSES OF FUO IN ADULTS

Habitual Hyperthermia
(Exaggerated circadian rhythm)

**Collagen
Vascular/Hypersensitivity
Diseases $\approx 19\%$**

Adult Still's disease
Behçet's disease
Erythema multiforme
Erythema nodosum
Giant-cell arteritis/polymyalgia
rheumatica
Hypersensitivity pneumonitis

Hypersensitivity vasculitis
Mixed connective-tissue disease
Polyarteritis nodosa
Relapsing polychondritis
Rheumatic fever
Rheumatoid arthritis
Schnitzler's syndrome
Systemic lupus erythematosus
Takayasu's aortitis
Weber-Christian disease
Granulomatosis with polyangiitis
(Wegener's)



CAUSES OF FUO IN ADULTS

Granulomatous Diseases

Crohn's disease
Granulomatous hepatitis
Midline granuloma
Sarcoidosis

Miscellaneous Conditions

Aortic dissection
Drug fever

Gout

Hematomas

Hemoglobinopathies

Laennec's cirrhosis

PFFPA syndrome: periodic fever, adenitis,
pharyngitis, aphthae

Postmyocardial infarction syndrome

Recurrent pulmonary emboli

Subacute thyroiditis (de Quervain's)

Tissue infarction/necrosis



CAUSES OF FUO IN ADULTS

Inherited and Metabolic Diseases

Adrenal insufficiency
Cyclic neutropenia
Deafness, urticaria, and amyloidosis
Fabry disease
Familial cold urticaria
Familial Mediterranean fever
Hyperimmunoglobulinemia D and periodic fever
Muckle-Wells syndrome
Tumor necrosis factor receptor-associated periodic syndrome (familial Hibernian fever)

Type V hypertriglyceridemia

Thermoregulatory Disorders

Central
Brain tumor
Cerebrovascular accident
Encephalitis
Hypothalamic dysfunction
Peripheral
Hyperthyroidism
Pheochromocytoma

Factitious Fevers

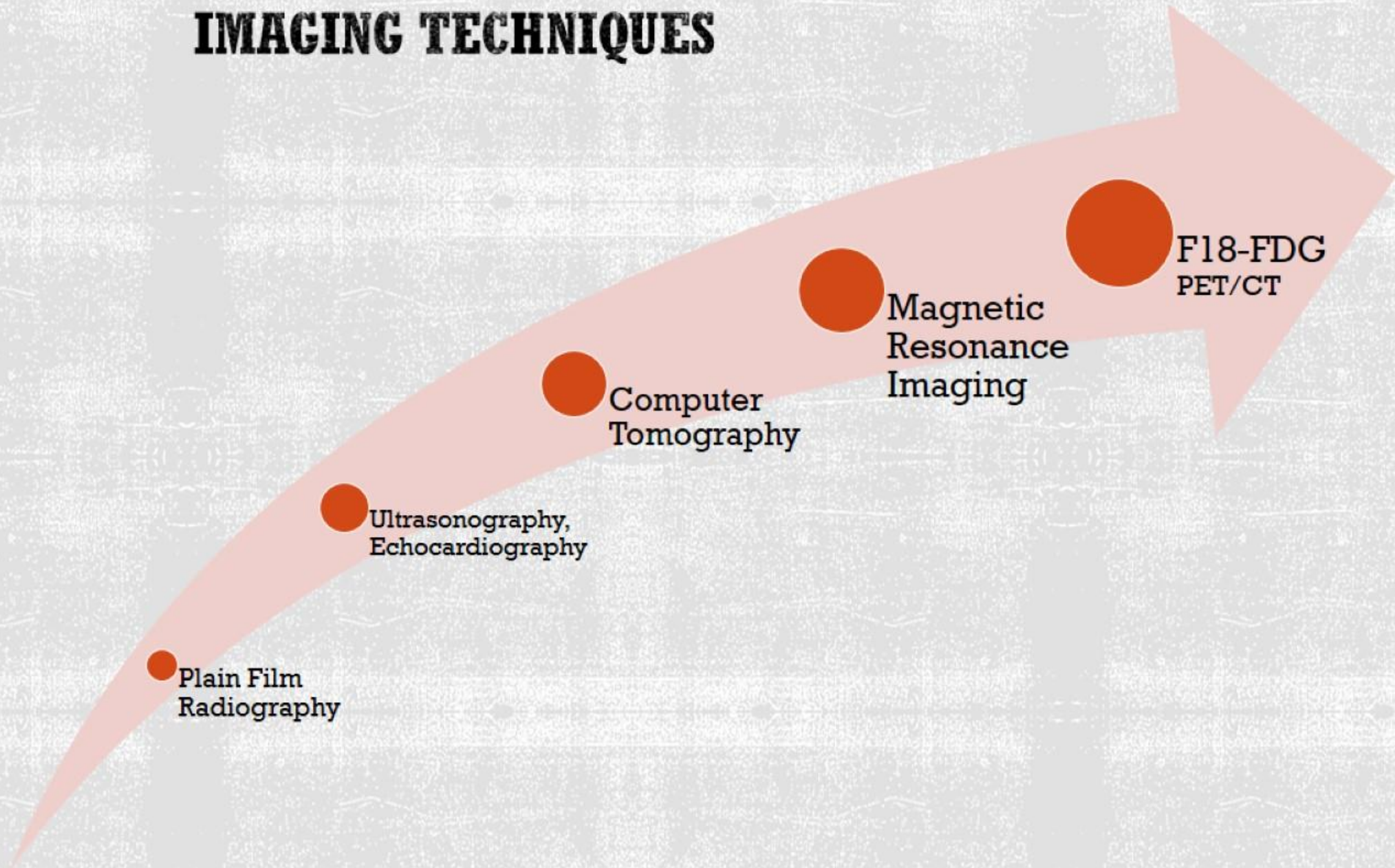
"Afebrile" FUO [$<38.3^{\circ}\text{C}$ (100.94°F)]



FEVER OF UNKNOWN ORIGIN OR FEVER OF TOO MANY ORIGINS?



IMAGING TECHNIQUES



Plain Film
Radiography

Ultrasonography,
Echocardiography

Computer
Tomography

Magnetic
Resonance
Imaging

F18-FDG
PET/CT



OTHER USEFUL PROCEDURES

Fundoscopy

Infections



Choroidal
lesions

Malignancies



Choroidal
metastases

Vasculitis



Cotton-wood
exsudates

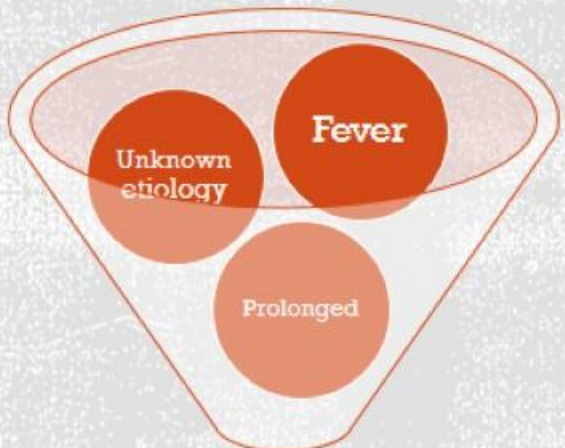
Sarcoidosis



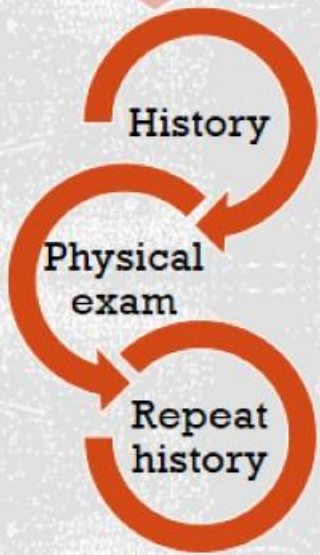
Perivascular
sheathing



DIAGNOSIS



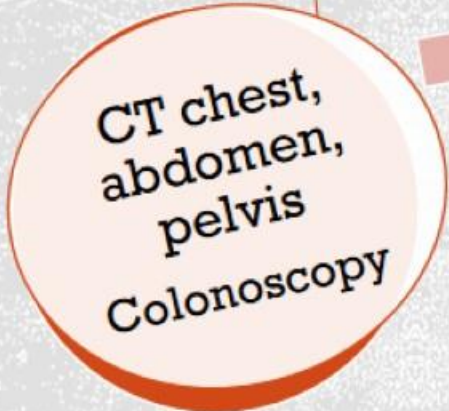
FUO



POTENTIALLY DIAGNOSTIC CLUES

No

Yes



+

-

+

-

-

+

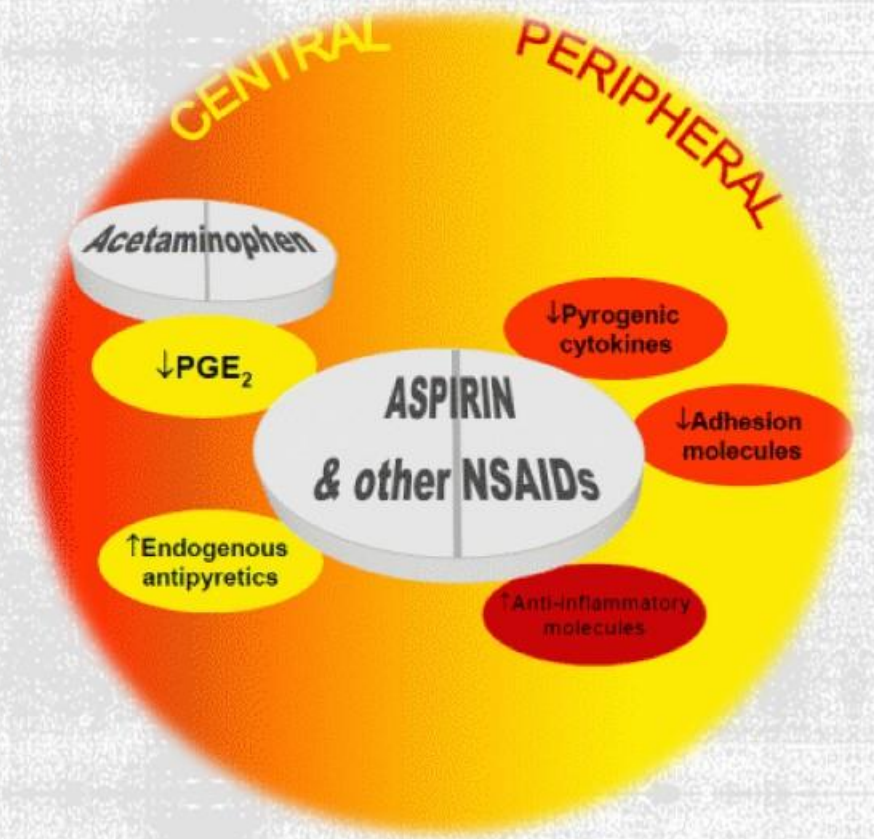


TREATMENT

Continued observation and examination

Antibiotic therapy

Vital-sign instability or neutropenia



OUTCOME, CONCLUSIONS

Many F/UO end up with no definitive diagnosis

About 50% of people without diagnosis improve within hospitalization or soon thereafter

15% have persistent fever that lasts at least 1 year

Rarely does death develop from fuo-five-year mortality of 3.2%.



NEW STUDIES

H. Balink et al. – A Rationale for the Use of F18-FDG PET/CT in Fever and Inflammation of Unknown Origin, International Journal of Molecular Imaging, 2012

Sherman JM et al. – Current challenges in the diagnosis and management of fever, Pediatr., 2012

Crouzet J et al.- Place of (18)F-FDG-PET with computed tomography in the diagnostic algorithm of patients with fever of unknown origin, Eur J Clin Microbiol Infect Dis, 2012

Manohar K et al.- F-18 FDG-PET/CT in evaluation of patients with fever of unknown origin, Jpn J Radiol, 2013

Nazar et al. -Spectrum of 18F-FDG PET/CT findings in patients presenting with fever of unknown origin, AJR, 2012



REVIEW STUDY

2001-
2007

- F 18-FDG PET
- 39% standalone
- 67% final diagnosis

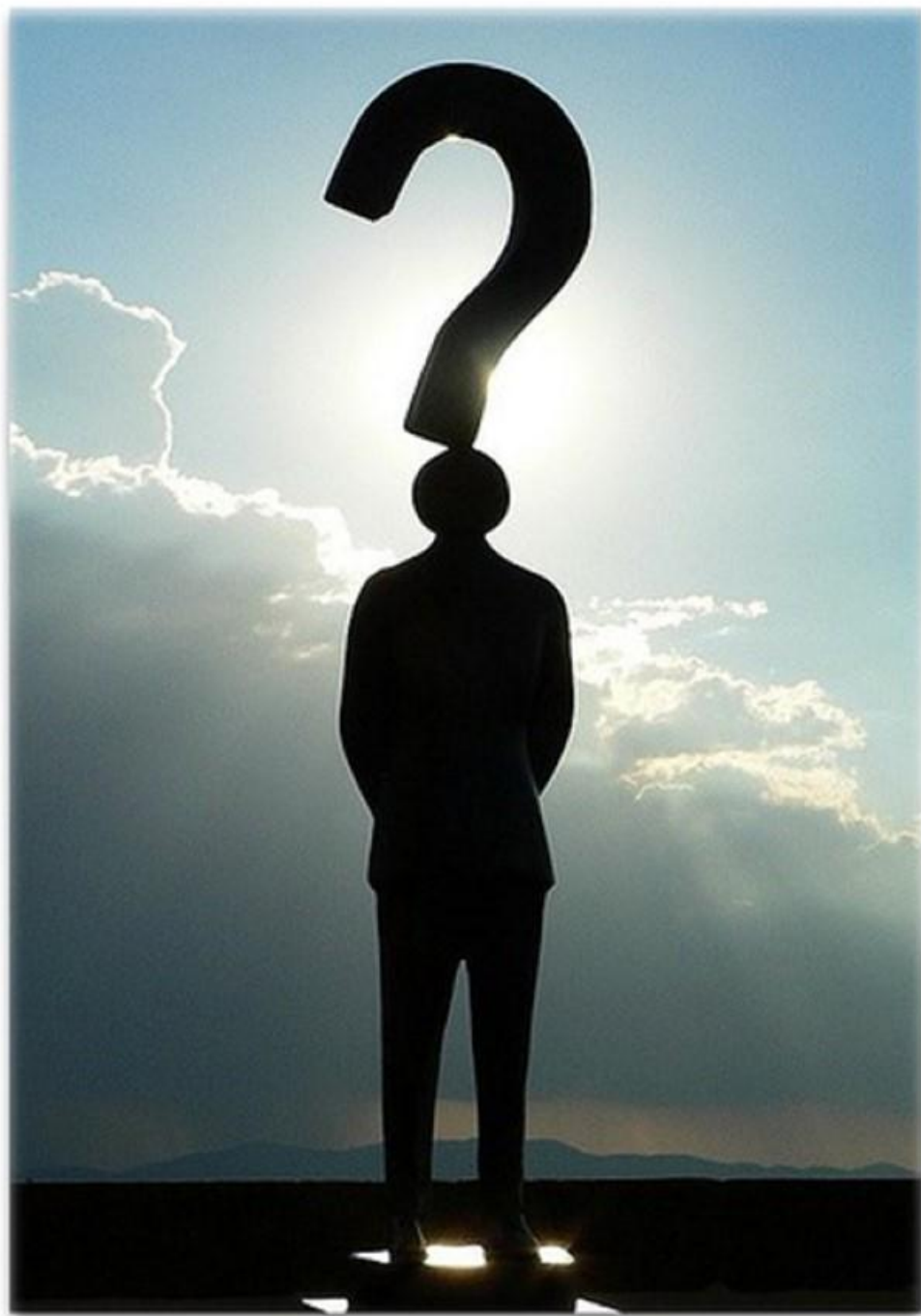
2008-
2012

- F 18-FDG PET/CT hybrid
- 57% standalone
- 73% final diagnosis



THE FUTURE





Thank you for your attention!

Happy Women's Day!

