

Fever of unknown origin (FUO)

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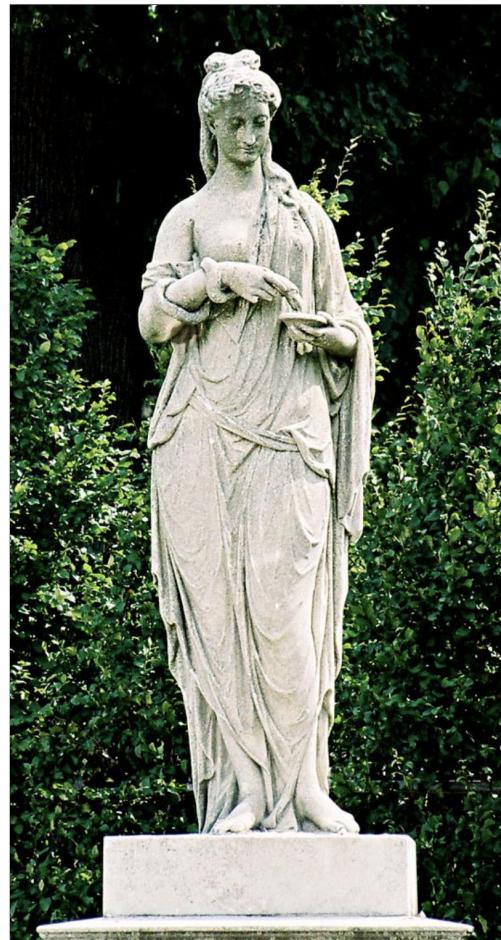
Objectives

- Recognize leading infectious causes of FUO in key patient groups
- Identify key fever patterns and clinical histories that may direct diagnosis
- Differentiate FUO risks and possible spectrum of pathogens in immunocompromised hosts

The history of fever

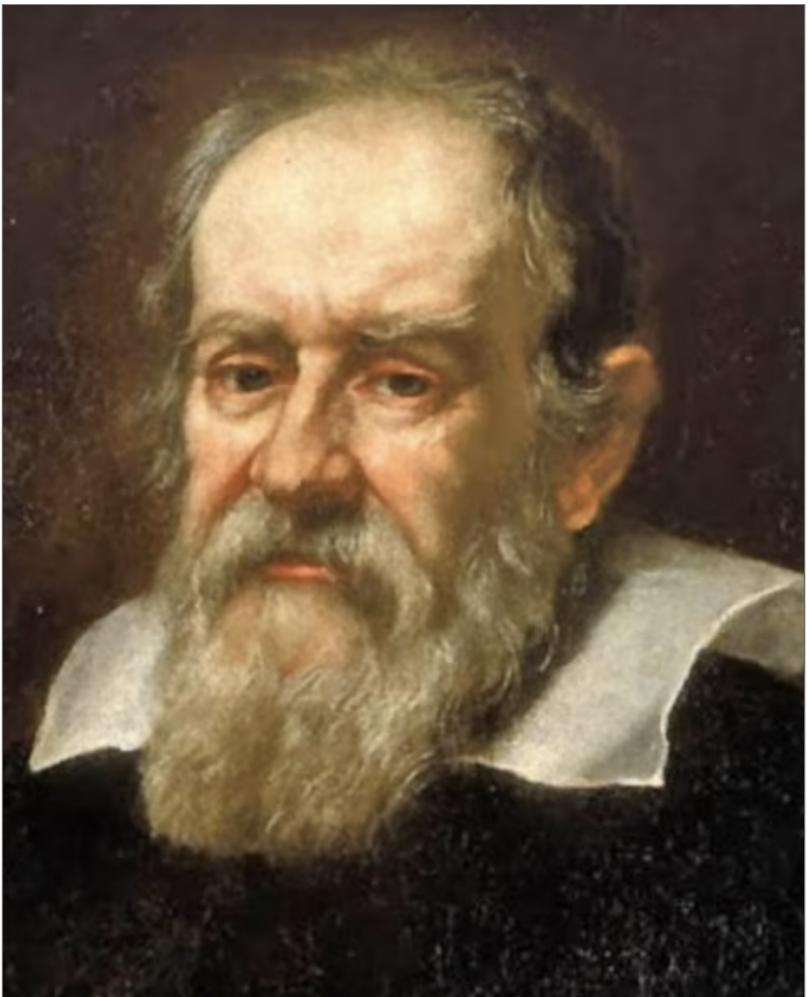
- **10th Century BCE Persian Physician Akhawayni** defined a system for fever curves in *Hidāyat al-Muta'allimīn fī al-Tibb* (The Student's Handbook of Medicine)
- **Hippocratic physicians** proposed that body temperature, and physiologic harmony in general, involved a delicate balance among four corporal humors—blood, phlegm, black bile, and yellow bile.
 - Fever was due to excess of yellow bile (many infections caused jaundice)
- **Galen:** many types of fever developed from putrification of humors.
- **Middle ages:** demonic possession
- **18th century (Harvey's discovery of circulation)**- friction of blood flow through body causing fermentation and putrification in intestines
- **Claude Bernard in the 19th century**- metabolic processes in the body

Febris- Roman Goddess of Fever



The legend of Febris was said to center around the haunting marshes of Camagna in Southern Italy where like clockwork every year, the people would become deathly ill with a mysterious disease. She was so feared by the Romans that the suffering population had created a cult to Febris. They went so far as to wear protective amulets and build her temples in order to worship her to win her favour.

Galileo and the room thermometer in Padova



Fever in modern medicine

- Wunderlich's pioneering studies of thermometry-normal 37°C
- Since the 19th century, humans have become gradually colder-0.05° to 0.5°C per decade
- Current normal range is 36.3 to 36.5°C

Fig. 81. Tertian.

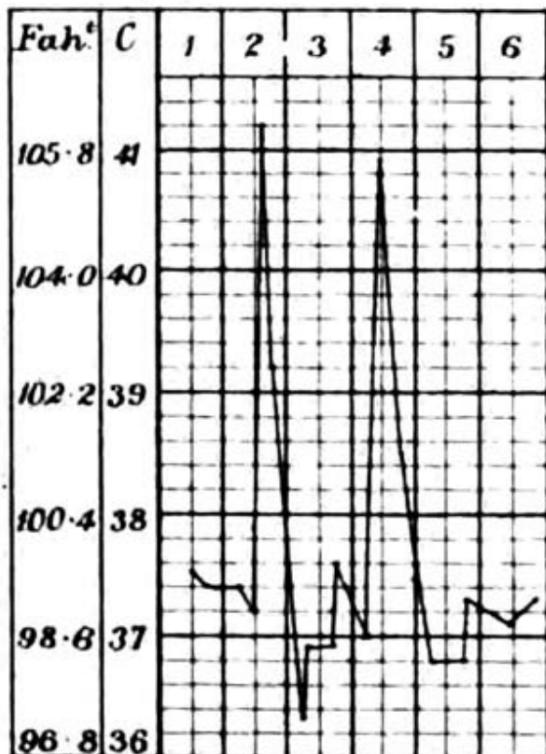
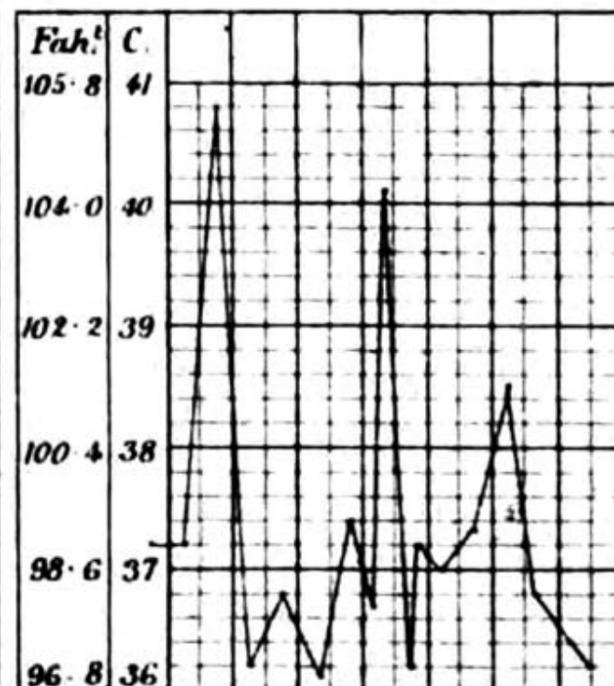
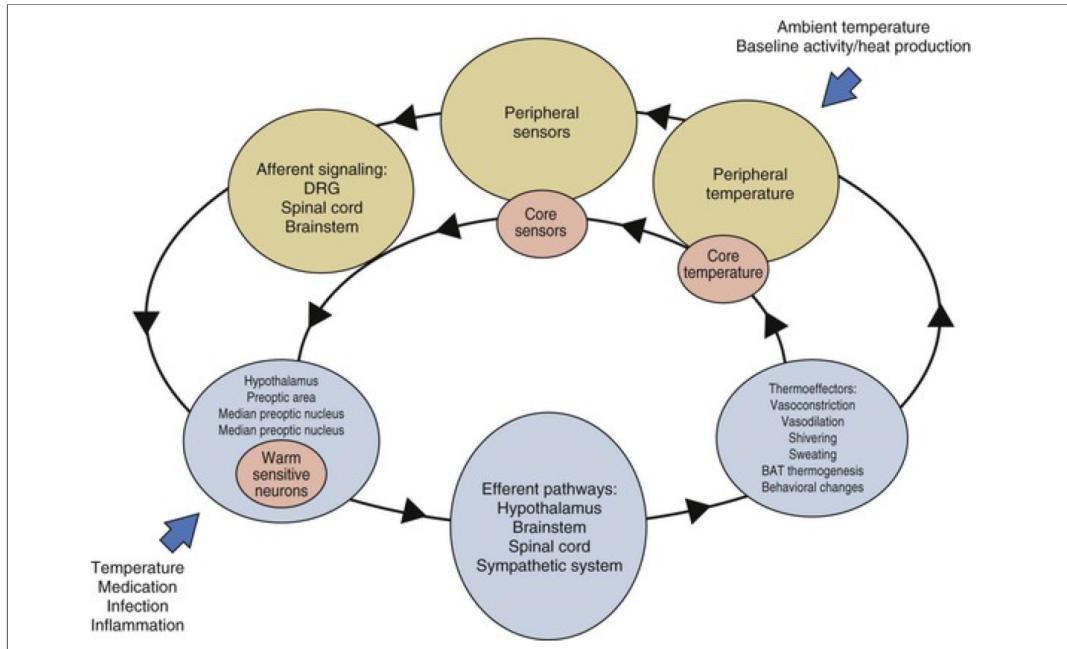


Fig. 82. Quartan.



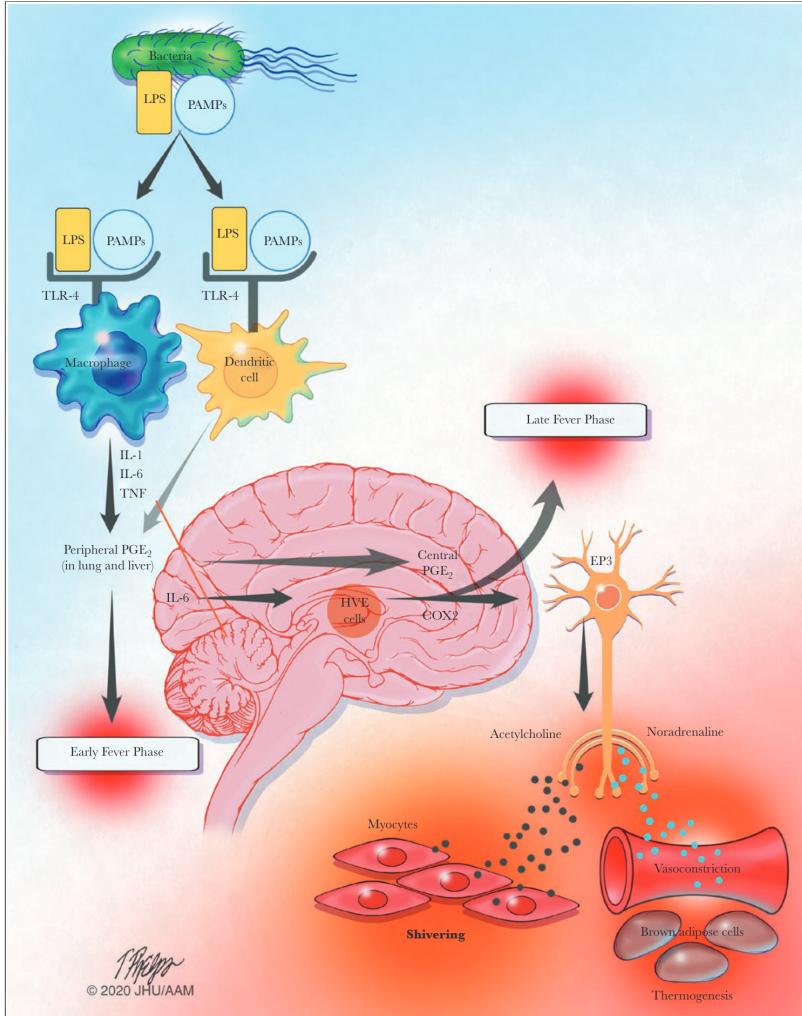
(Mackowiak and Worden, 1994)

Thermal homeostasis



([Sajadi, Mohammad M. and Mackowiak, Philip A., n.d.](#))

Infection-associated fever



(Wright and Auwaerter, 2020)

Sequelae of fever

- Phylogenetic conservation of fever over the millennia suggests fever is beneficial
- Most pathogenic bacteria are mesophiles (35°C ideal for growth)
- Fever generates hepatic iron-sequestering compounds that bind free iron necessary for microbial replication

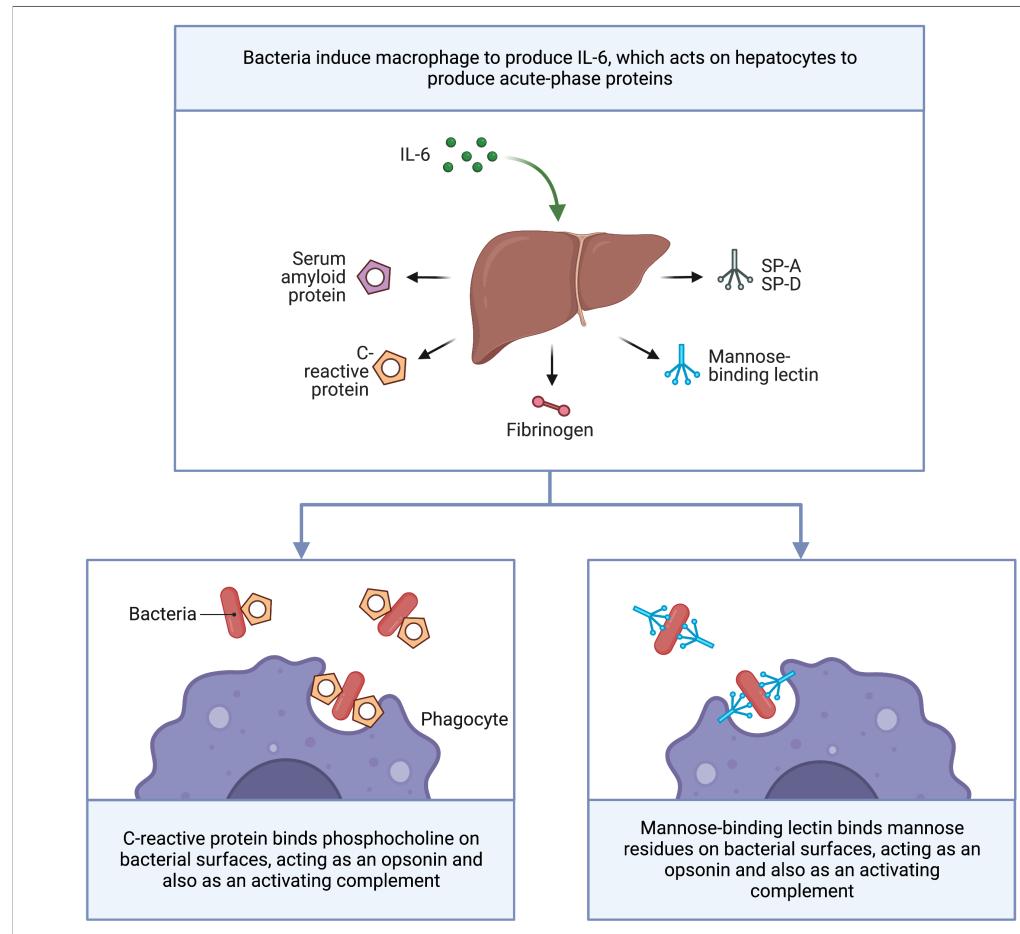
Acute phase proteins

TABLE 1. HUMAN ACUTE-PHASE PROTEINS.

| Proteins whose plasma concentrations increase | |
|---|--|
| Complement system | |
| C3 | |
| C4 | |
| C9 | |
| Factor B | |
| C1 inhibitor | |
| C4b-binding protein | |
| Mannose-binding lectin | |
| Coagulation and fibrinolytic system | |
| Fibrinogen | |
| Plasminogen | |
| Tissue plasminogen activator | |
| Urokinase | |
| Protein S | |
| Vitronectin | |
| Plasminogen-activator inhibitor 1 | |
| Antiproteases | |
| α_1 -Protease inhibitor | |
| α_1 -Antichymotrypsin | |
| Pancreatic secretory trypsin inhibitor | |
| Inter- α -trypsin inhibitors | |
| Transport proteins | |
| Ceruloplasmin | |
| Haptoglobin | |
| Hemopexin | |
| Participants in inflammatory responses | |
| Secreted phospholipase A ₂ | |
| Lipopolysaccharide-binding protein | |
| Interleukin-1-receptor antagonist | |
| Granulocyte colony-stimulating factor | |
| Others | |
| C-reactive protein | |
| Serum amyloid A | |
| α_1 -Acid glycoprotein | |
| Fibronectin | |
| Ferritin | |
| Angiotensinogen | |
| Proteins whose plasma concentrations decrease | |
| Albumin | |
| Transferrin | |
| Transthyretin | |
| α_2 -HS glycoprotein | |
| Alpha-fetoprotein | |
| Thyroxine-binding globulin | |
| Insulin-like growth factor I | |
| Factor XII | |

(Gabay and Kushner, 1999)

Role of acute phase proteins



Acute phase phenomena

TABLE 2. OTHER ACUTE-PHASE PHENOMENA.

| |
|---|
| Neuroendocrine changes |
| Fever, somnolence, and anorexia |
| Increased secretion of corticotropin-releasing hormone, corticotropin, and cortisol |
| Increased secretion of arginine vasopressin |
| Decreased production of insulin-like growth factor I |
| Increased adrenal secretion of catecholamines |
| Hematopoietic changes |
| Anemia of chronic disease |
| Leukocytosis |
| Thrombocytosis |
| Metabolic changes |
| Loss of muscle and negative nitrogen balance |
| Decreased gluconeogenesis |
| Osteoporosis |
| Increased hepatic lipogenesis |
| Increased lipolysis in adipose tissue |
| Decreased lipoprotein lipase activity in muscle and adipose tissue |
| Cachexia |
| Hepatic changes |
| Increased metallothionein, inducible nitric oxide synthase, heme oxygenase, manganese superoxide dismutase, and tissue inhibitor of metalloproteinase-1 |
| Decreased phosphoenolpyruvate carboxykinase activity |
| Changes in nonprotein plasma constituents |
| Hypozincemia, hypoferrremia, and hypercupremia |
| Increased plasma retinol and glutathione concentrations |

(Gabay and Kushner, 1999)

Epidemiology of FUO- Definitions

Table 1. Broad Categories of Fever of Unknown Origin (FUO).*

| Category | Definition and Causes |
|---|---|
| Classic FUO | FUO despite reasonable initial investigations in the inpatient or outpatient setting; includes FUO in persons with HIV infection who are virally suppressed, with CD4 counts >200 cells/mm ³ ; causes fall into four categories: infections (e.g., tuberculosis, endocarditis, occult abscesses, Whipple's disease, enteric fever, syphilis [mainly secondary], various zoonoses, and histoplasmosis), cancer, autoimmune and autoinflammatory disorders, and miscellaneous causes |
| Nosocomial FUO | FUO that develops in hospitalized persons |
| ICU patients | Causes include infections (bacteremia, pneumonia, <i>Clostridioides difficile</i> infection, fungemia, catheter-associated infections, decubitus ulcers), thromboembolic events, acalculous cholecystitis, drug-associated fever, strokes, cerebral hemorrhages, and bleeding |
| Non-ICU patients | Similar causes to those listed for FUO in ICU setting, although patients are not critically ill |
| Immunodeficiency-associated FUO | Causes are highly variable, depending on the type of underlying immunodeficiency |
| Organ-transplant recipients | Causes include viruses, donor-derived infections, <i>Strongyloides stercoralis</i> hyperinfection, opportunistic fungal infections, rejection, and in rare cases, GVHD, graft intolerance syndrome (from retained kidney grafts in situ after graft failure), old nonfunctioning arteriovenous grafts after kidney transplantation (may cause occult infection or fever), hemophagocytic lymphohistiocytosis, and ureaplasma-related hyperammonemia syndrome |
| Patients with neutropenia | High-risk patients with neutropenia are considered to have FUO if they have been febrile for >5 days despite appropriate empirical antibiotic therapy, etiologic diagnosis affected by duration of neutropenia, immunosuppression for GVHD treatment or prophylaxis, and prophylactic antimicrobial therapy |
| Hematopoietic-cell transplant recipients | Causes before engraftment: similar to causes of neutropenic FUO Causes in early period after engraftment: engraftment itself, opportunistic herpesvirus infections, adenovirus infection, hyperacute GVHD, infectious pneumonia, idiopathic pneumonia syndrome Causes in late period after engraftment: multiple causes, including relapsed cancer; immune reconstitution is not fully restored for approximately 24 mo, and patients remain at risk for infection (e.g., from encapsulated organisms) during that period |
| Patients with HIV infection not receiving ART, patients with AIDS | Causes include acute retroviral syndrome, mycobacterial infection, endemic mycoses, toxoplasmosis, cryptococcosis, HHV-8 infection (e.g., Kaposi's sarcoma, primary effusion lymphoma, Kaposi's sarcoma herpesvirus inflammatory cytokine syndrome), and lymphoma |
| Travel-associated FUO | Causes include malaria, enteric fever, leptospirosis, viral hemorrhagic fevers, typhus, and acute undifferentiated febrile illness of tropical countries ²⁴ |

* The table includes a selected list of entities that may be associated with FUO. Data are from Durack and Street³ and Wright and Auwaerter.²³ AIDS denotes acquired immunodeficiency syndrome, ART antiretroviral therapy, GVHD graft-versus-host disease, HHV human herpesvirus, HIV human immunodeficiency virus, and ICU intensive care unit.

(Haidar and Singh, 2022)

Classic FUO

- **Definition:**

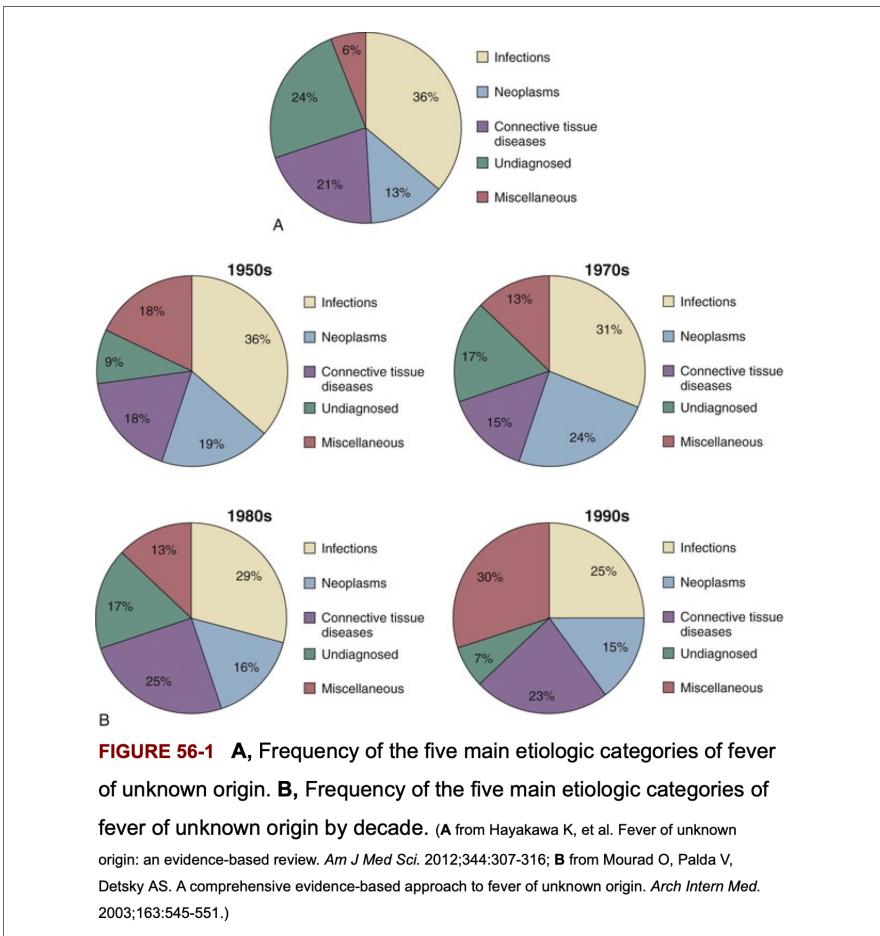
- Temperature of $> 38.3^{\circ}\text{C}$ > 3 weeks
- Fever > 2 separate outpatient visits with diagnostic investigations *or*
- Fever > 2 visits in hospital of 3 days with diagnostic investigations
 - *However, these definitions are largely subjective*

- **Leading causes:**

- Infections (geography dependent)
- Inflammatory conditions (age dependent)
- Cancer (age dependent)
- Undiagnosed /unknown

Frequency of the 5 main etiologic categories of FUO

Infectious causes decrease in patients above age 65 years



(Wright, William F. and Mackowiak, Philip A., 2015)

Classic FUO- Infectious Etiology

- Chronic or relapsing infections
 - Occult abscess
 - Endocarditis
 - Tuberculosis
 - Complicated urinary tract infections
 - Osteomyelitis

Classic FUO work-up

- **Medical history emphasis:**
 - Travel
 - Contacts
 - Animal and insect exposure
 - Medications
 - Immunizations
 - Family history
 - Cardiac valve disorder
- **Examination emphasis**
 - Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower limb deep veins
- **Investigation emphasis:**
 - Imaging, biopsies, sedimentation rate, skin tests

Rare and miscellaneous causes of fever

| | |
|---|-------------------------------------|
| Addison's disease | Infected urachal cyst |
| Adult-onset Still's disease | Inflammatory bowel disease |
| Alcoholic hepatitis | Kikuchi-Fujimoto disease |
| Allergic alveolitis | Lofgren syndrome |
| Aortic dissection | Lymphomatoid granulomatosis |
| Aortitis | Metal fume fever |
| Atrial myxoma | Myeloproliferative syndromes |
| Autoimmune cholangitis | Pancreatitis |
| Bartonellosis | Parathyroid apoplexy |
| Behçet's syndrome | Paroxysmal hemoglobinurias |
| Carcinomatous meningitis | Pericarditis |
| Castleman's disease | Periodic fever |
| Chronic meningitis | Pheochromocytoma |
| Cirrhotic fever | Polyarteritis nodosa |
| Cyclic neutropenia | Postpericardiotomy syndrome |
| Drug fever and other hypersensitivities | Pulmonary emboli |
| Erythema multiforme | Resorbing hematoma |
| Fabry's disease | Retroperitoneal fibrosis |
| Factitious fever | Rosai-Dorfman disease |
| Familial Hibernian fever | Sarcoidosis |
| Familial Mediterranean fever | Schnitzler's syndrome |
| Giant coronary aneurysm | Sinusitis |
| Granulomatous hepatitis | Serum sickness |
| Granulomatous peritonitis | Sjögren's syndrome |
| Hantavirus infection | Subacute necrotizing lymphadenitis |
| Hemoglobinopathies | Thrombotic thrombocytopenic purpura |
| Hemolytic anemias | Thyroiditis and thyrotoxicosis |
| Hemophagocytic syndrome | Veno-occlusive disease |
| Histiocytosis X | Vitamin B ₁₂ deficiency |
| Human picornavirus infection | Wegener's granulomatosis |
| Hypereosinophilic syndrome | Whipple's disease |
| Immunoblastic lymphadenopathy | |

Classic FUO in infants and children

- Respiratory tract infections
- Other infections: UTIs, brucellosis, tuberculosis, bartonellosis
- Kawasaki disease (age < 5 years)
- Inflammatory bowel diseases
- Still's disease (juvenile rheumatoid arthritis)
 - However, connective tissue diseases and cancers are generally rare in children
- Joint involvement is an important sign of a potentially serious disorder- e.g., *connective tissue disease, endocarditis, leukemia*

Classic FUO in elderly patients

- In developed countries: connective tissue diseases > infections
 - Temporal arteritis
 - Polymyalgia rheumatic syndromes
- Diagnoses are frequently missed because symptoms are subacute and non-specific
- Infections
 - intraabdominal abscess
 - Complicated UTIs
 - Tuberculosis
 - Endocarditis

Returning travellers

| DIAGNOSIS | PERCENTAGE | |
|--|--|--|
| | Maclean et al ⁹¹ (n = 587) | Doherty et al ⁹² (n = 195) |
| Malaria | 32 | 42 |
| Hepatitis | 6 | 3 |
| Respiratory tract infection* | 11 | 2.6 |
| Urinary tract infection/pyelonephritis | 4 | 2.6 |
| Dysentery | 4.5 | 5.1 |
| Dengue fever | 2 | 6.2 |
| Enteric fever | 2 | 1.5 |
| Tuberculosis | 1 | 2 |
| Rickettsial infection | 1 | 0.5 |
| Acute HIV infection | 0.3 | 1.0 |
| Amebic liver abscess | 1 | 0 |
| Other miscellaneous infections | 4.3 | 9.2 |
| Miscellaneous noninfectious causes | 6 | 1 |
| Undiagnosed | 25 | 24.6 |

(Wright, William F. and Mackowiak, Philip A., 2015)

Nosocomial (Health-Care Associated) FUO

- **Leading causes:**

- Drug fever
- Post-operative complications (e.g., occult abscess)
- Decubitus ulcers
- Septic thrombophlebitis
- Recurrent pulmonary emboli
- Myocardial infarction
- Cancer
- Blood transfusion
- Reactions to contrast media
- *Clostridium difficile* colitis

Fever in post-operative patients

- Although more than 1/3 of patients may manifest fever in first 5 days surgery, < 10% of febrile patients have an identified source or positive cultures
- Fever may represent a physiological response to surgically-induced tissue injury with release of pyrogenic cytokines and interleukins rather than result of infection

FUO in ICU patients

- Early fevers are common, often non-infectious, associated with good prognosis
- Prolonged fever carries a poorer prognosis
- Sinusitis as a complication of mechanical ventilation, supine position, feeding tubes
- Other causes are similar to nosocomial infections in non-ICU patients
 - Abscess
 - Drug fever
 - Postoperative complications
 - Septic thrombophlebitis
 - Recurrent pulmonary emboli
 - Myocardial infarction

FUO in stroke patients

- Non-infective fevers are commonly seen in patients with intracranial mass effects and occur earlier after stroke than infection
- UTI are common related to urinary catheterization

FUO in neutropenic patients

- ANC= Total WBC x (% Segs + % Bands)
- Neutropenia is defined as an ANC of < 500 cells/mm³ or an ANC that is expected to decrease to < 500 cells/mm³ during the next 48 h.
 - The term “profound” is sometimes used to describe neutropenia in which the ANC is < 100 cells/mm³
- Fever occurs frequently during chemotherapy-induced neutropenia:
 - 10%–50% of patients with solid tumors
 - 80% of those with hematologic malignancies will develop fever during >1 chemotherapy cycle associated with neutropenia
- Most patients will have no infectious etiology documented.
- Signs of inflammation are notoriously absent other than fever

Clinical manifestations of infection related to absolute neutrophil count (ANC)

| Signs and symptoms | Infection | % of patients with ANC< 100 | % of patients with ANC>1000 |
|--------------------|-----------|-----------------------------|-----------------------------|
| Fever | Overall | 98 | 76 |
| Bacteremia | Overall | 43 | 13 |
| Fluctuance | Anorectal | 8 | 67 |
| Exudate | Skin | 5 | 92 |
| Purulent sputum | Pneumonia | 8 | 84 |
| Pyuria | UTI | 11 | 97 |

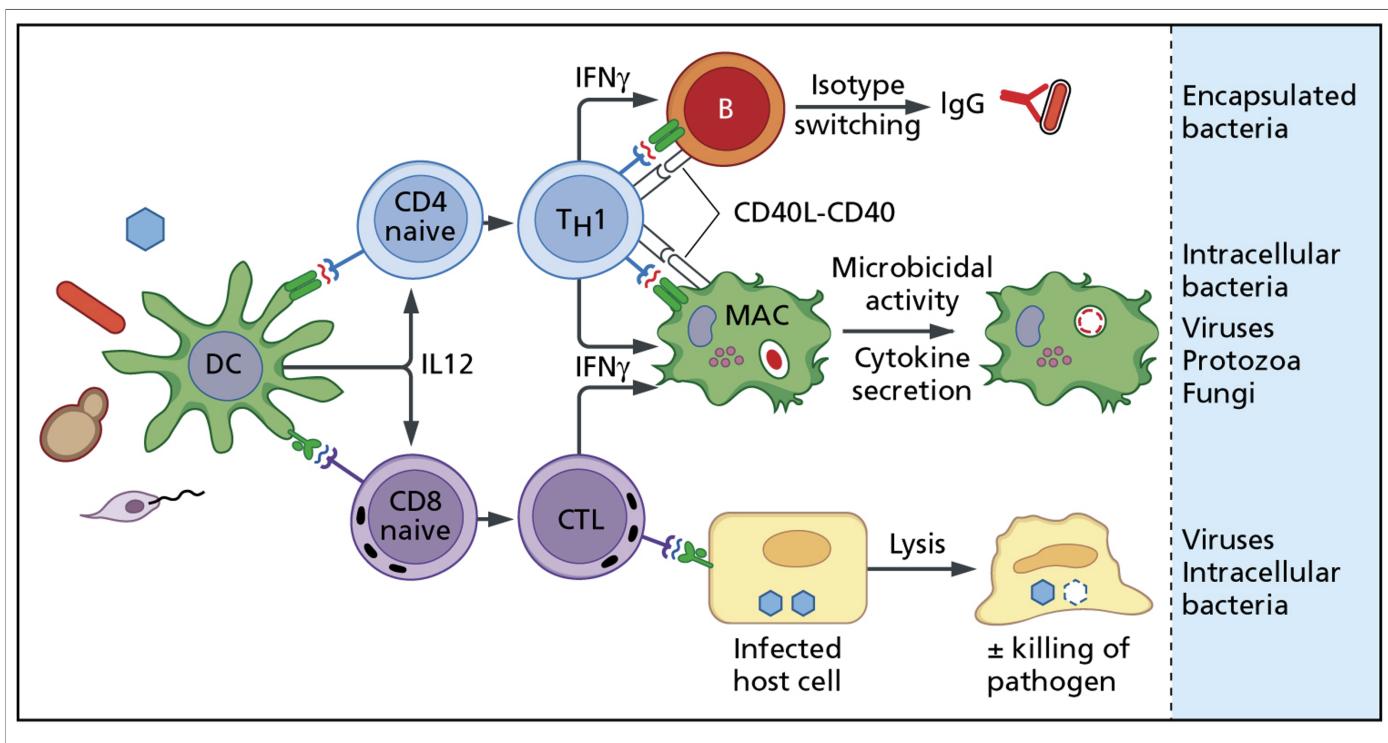
(Sickles et al., 1975)

Possible causes of fever in neutropenic patients not responding to broad-spectrum antibiotics

| CAUSES | APPROXIMATE FREQUENCY IN HIGH-RISK PATIENTS (%) |
|---|---|
| Fungal infections susceptible to empirical therapy | 40 |
| Fungal infections resistant to empirical antifungal therapy | 5 |
| Bacterial infections (with cryptic foci, biofilms, and resistant organisms) | 10 |
| <i>Toxoplasma gondii</i> , mycobacteria, or fastidious pathogens (<i>Legionella</i> , <i>Mycoplasma</i> , <i>Chlamydia pneumoniae</i> , <i>Bartonella</i>) | 5 |
| Viral infections (herpesviruses, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, varicella-zoster virus, herpes simplex virus, parainfluenza virus, respiratory syncytial virus, influenza viruses) | 5 |
| Graft-versus-host disease after hematopoietic stem cell transplantation | 10 |
| Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens) | 25 |

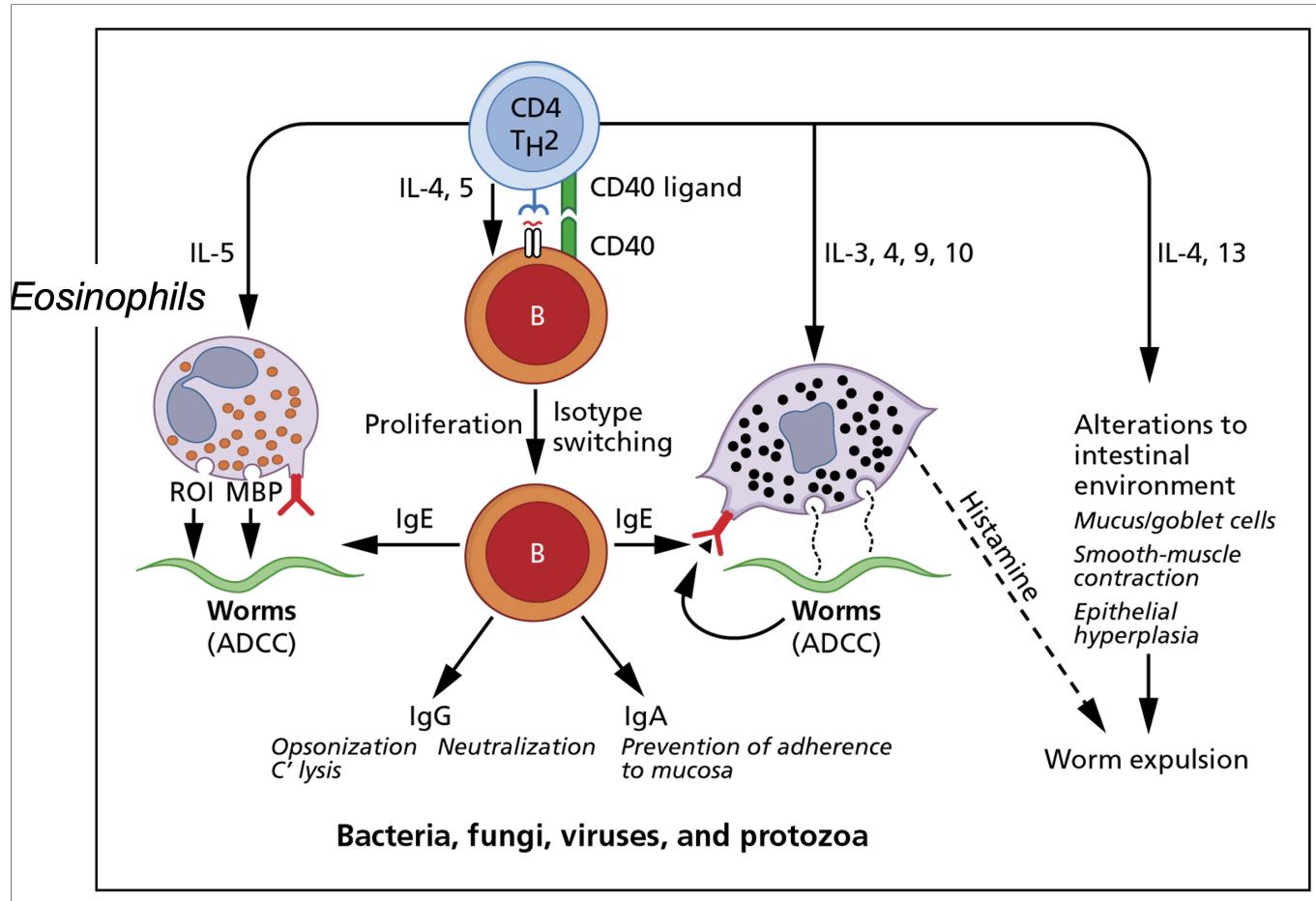
(Corey and Boeckh, 2002)

Cell-mediated immunity-1



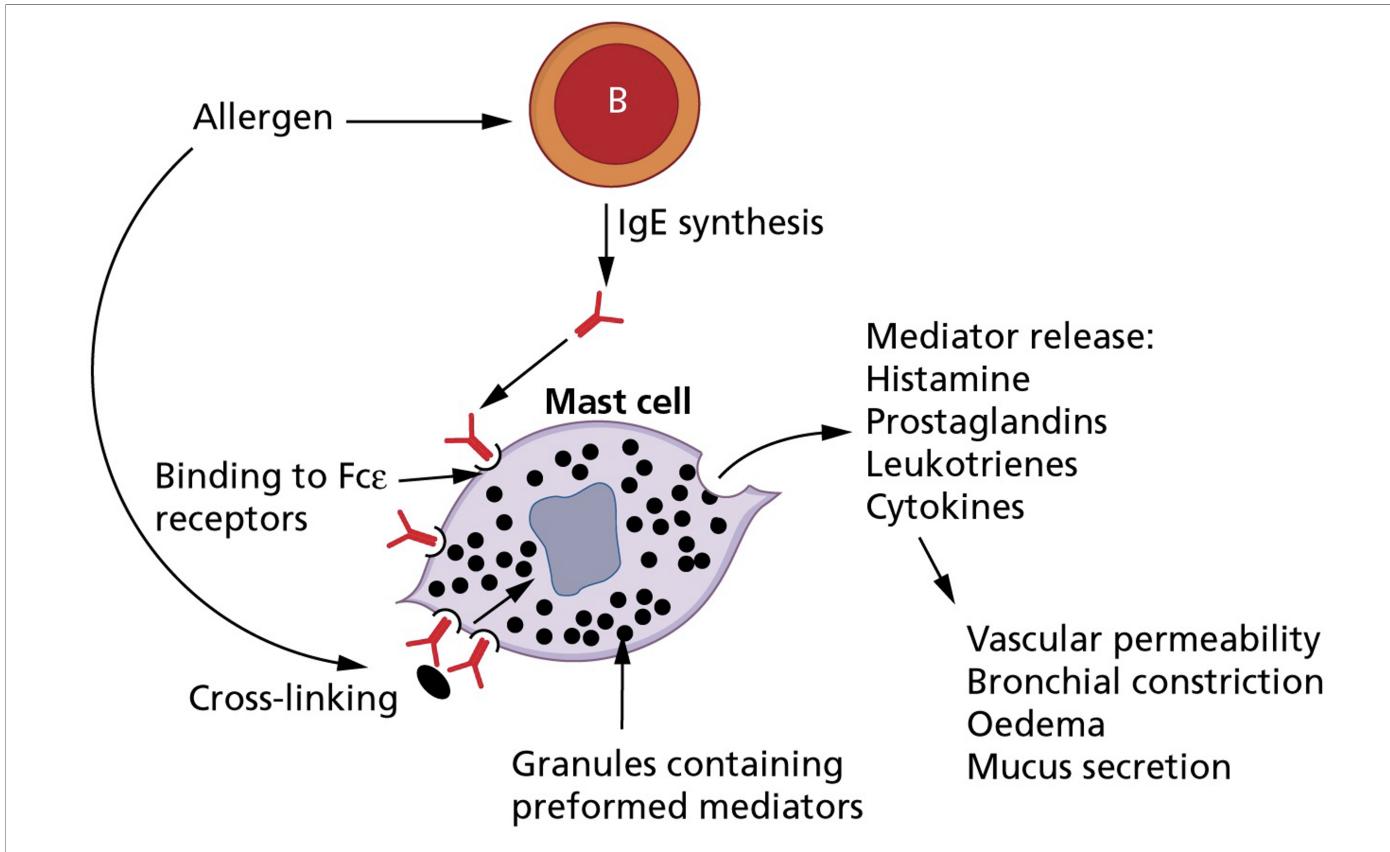
(Playfair, J. and Bancroft, G., 2013)

Cell-mediated immunity-2



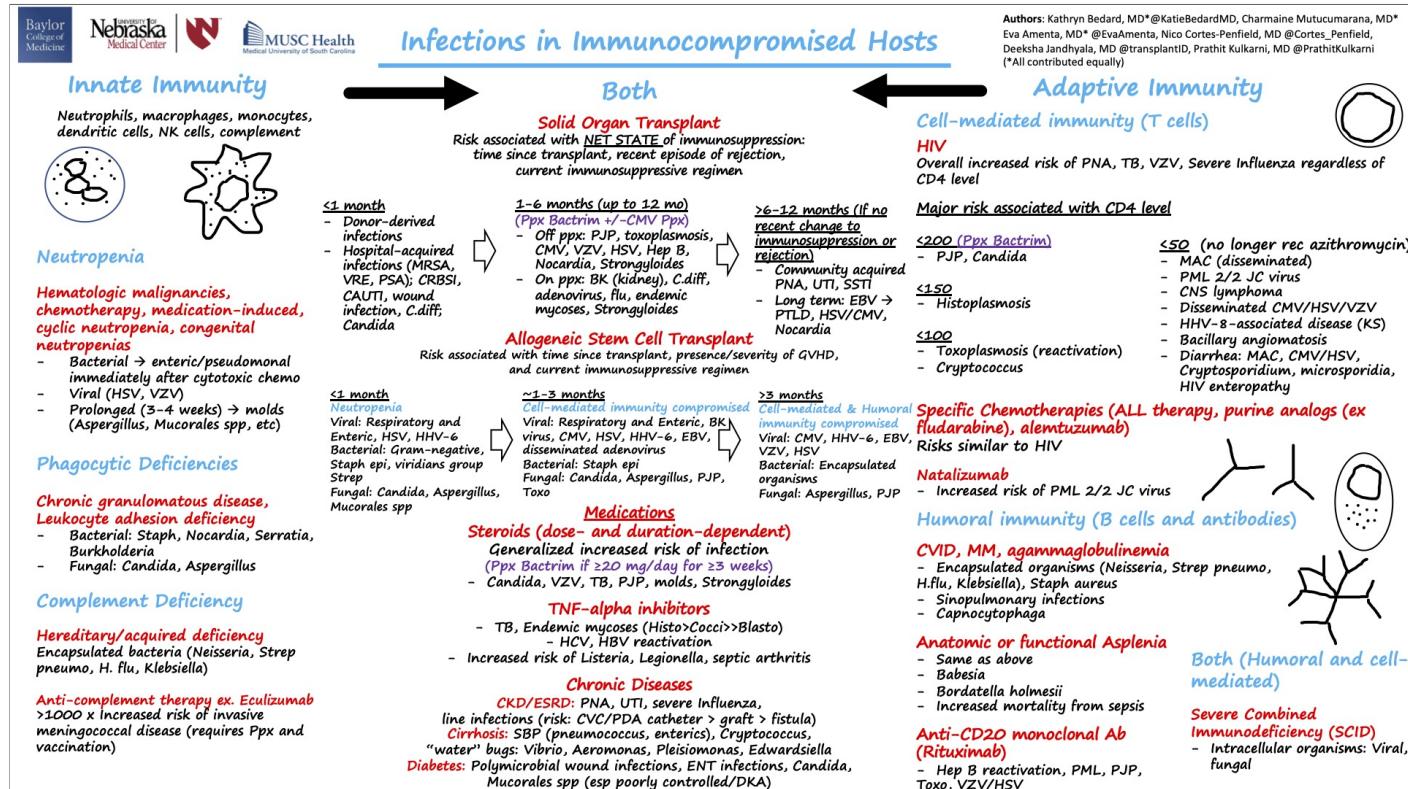
(Playfair, J. and Bancroft, G., 2013)

Cell-mediated immunity-Drug allergy



(Playfair, J. and Bancroft, G., 2013)

Infections in immunocompromised hosts



HIV-related FUO

- Primary phase of infection characterized by mononucleosis-like illness where fever is common, may be undiagnosed if it precedes seroconversion
- In later phases of untreated HIV, episodes of fever become common and often signify a superimposed illness- e.g., opportunistic infections that manifest in atypical fashion
- Once highly-active antiretroviral therapy (HAART) is started and HIC viral load is effectively suppressed, the frequency of FUO falls markedly

Etiology of fever in HIV-Associated FUO (n=70)

| ETOIOLOGY | NO. (%) OF TIMES DIAGNOSIS WAS ESTABLISHED |
|---|--|
| Infection | |
| DMAC | 22 (31) |
| <i>Pneumocystis jirovecii</i> pneumonia | 10 (13) |
| CMV | 8 (11) |
| Histoplasmosis | 5 (7) |
| Viral (not CMV)* | 5 (7) |
| Bacterial | 4 (5) |
| <i>Mycobacterium tuberculosis</i> | 4 (5) |
| Fungal (not histoplasmosis)*† | 2 (3) |
| Parasitic*‡ | 2 (3) |
| <i>Mycobacterium genavense</i> | 1 (1) |
| Total | 63 (88) |
| Neoplasia | |
| Lymphoma | 5 (7) |
| Kaposi sarcoma | 1 (1) |
| Total | 6 (8) |
| Miscellaneous | |
| Drug fever | 2 (3) |
| Castleman disease | 1 (1) |
| Total | 3 (4) |

([Wright, William F. and Mackowiak, Philip A., 2015](#))

Naproxen (NSIAD) fever suppression test for “tumor fever”

- A trial of naproxen may differentiate neoplastic from non-neoplastic fever
 - Temperature $>37.8^{\circ}\text{C}$ at least once a day;
 - Duration of fever >2 weeks;
 - Lack of evidence of infection (eg physical examination, laboratory examinations, and imaging studies);
 - Absence of allergic mechanisms (eg, drug allergy, transfusion reaction, and radiation or chemotherapeutic drug reaction);
 - Lack of response of fever to an empiric, adequate antibiotic therapy for at least 7 days;
 - Prompt complete lysis by the naproxen test with sustained normal temperature while receiving naproxen.

Diagnosis of FUO

General diagnostic evaluation of FUO

Comprehensive history

Repeated physical exams

Complete blood count

Routine blood chemistry

Urinalysis including microscopic examination

Chest radiograph

Erythrocyte sedimentation rate, C-reactive protein

Antinuclear antibodies

Rheumatoid factor

Blood cultures- three separate specimens in the absence of antimicrobial therapy

CMV IgM antibodies or viral detection in blood

Heterophil antibody test in children and young adults

Tuberculin skin test

Computed tomography of abdomen, pelvis and other sites

MRI/Radionucleotide scans

HIV antibodies or viral detection assay

Further evaluation of any abnormality detected by above tests

Various duplex imaging of lower limbs

([Wright, William F. and Mackowiak, Philip A., 2015](#))

Patient history

- Helps guide choice of initial laboratory investigations
- Particular attention should be given to:
 - Recent travel
 - Exposure to pets and other animals
 - Work environment
 - Recent contact with people with similar symptoms
 - Family history (e.g., familial Mediterranean fever)
- Prior history of FUO
- Previously diagnosed conditions
 - Lymphoma
 - Rheumatic fever
 - Intraabdominal disorders
- Complete list of medications

Verification of fever and fever pattern

- Obvious,... but often overlooked
 - In some series, up to 30% referred for FUO where determined to not have fever
- Fever patterns- arcane terminology:
 - *remittent, intermittent, hectic, quotidian, sustained, quartan, saddleback fevers*
- Fever patterns are affected by:
 - Hydration, ambient temperature
 - Accuracy of temperature measurements
 - Use of antipyretics, corticosteroids
 - Blood transfusions, other medical interventions etc.

Continuous sustained fever

- Continuous (sustained) fever with slight remission not exceed 2°C
 - Lobar and Gram negative pneumonia
 - Rickettsiosis
 - Typhoid fever
 - CNS disorders
 - Tularemia
 - Falciparum (malignant tertian) malaria

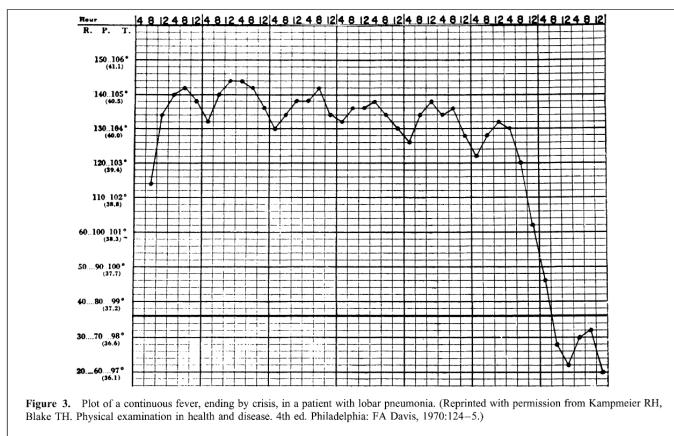
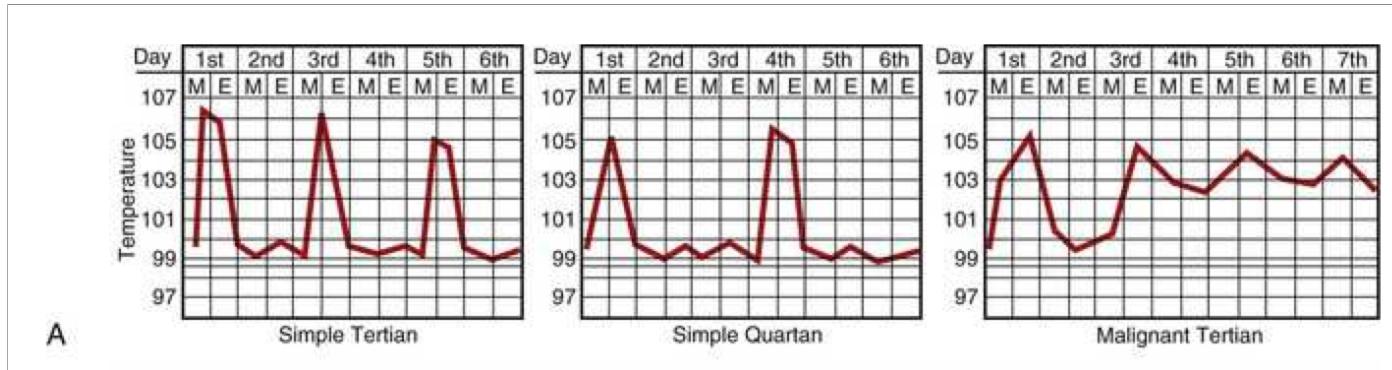


Figure 3. Plot of a continuous fever, ending by crisis, in a patient with lobar pneumonia. (Reprinted with permission from Kampmeier RH, Blake TH. Physical examination in health and disease. 4th ed. Philadelphia: FA Davis; 1970:124–5.)

([Mackowiak et al., 1997](#))

Malaria fever



Febrile paroxysms may occur every other day for *P. vivax*, *P. ovale*, and *P. falciparum* and every third day for *P. malariae*. Paroxysms occurring at regular intervals are more common in the setting of infection due to *P. vivax* or *P. ovale* than *P. falciparum*. With improvements in early diagnosis and treatment, this traditional description of cyclic fever is seen infrequently.

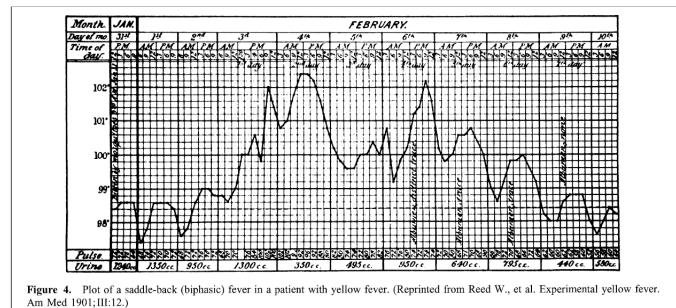
Intermittent fever

- Intermittent (septic, quotidian, “picket fence”) fever with wide fluctuations, usually normal or low in the morning and peaking between 4:00 and 8:00 PM
 - Localized pyogenic infections and bacterial endocarditis with chills and leukocytosis
 - Malaria (often with leukopenia) may present with daily (quotidian) daily spike or (tertian) spike every 3rd day, or (quartan) spike every 4th day.
 - Double quotidian pattern (two daily spikes) seen with salmonellosis, miliary tuberculosis, double malarial infections (more than one species), gonococcal and meningococcal endocarditis

(Mackowiak et al., 1997)

Saddle-back (biphasic)

- Several days of fever, distinct reduction in fever for ~ 1 day, and then several days of higher fever
 - Dengue and yellow fever
 - Colorado tick fever
 - Rift valley Fever
 - Influenzae and other viral infections



(Mackowiak et al., 1997)

Intermittent hectic (Charcot's) fever

- Sporadic episodes of fever, periods of normal temperature with recurrence
 - Frequently seen in cholangitis associated with cholelithiasis, jaundice, leukocytosis and toxic signs

(Mackowiak et al., 1997)

Pel-Ebstein fever

- Weekly or longer periods of fever and equally long afebrile periods, with repetition of the cycle
 - Hodgkin's disease
 - Brucellosis due to *Brucella melitensis*
 - Occasionally tuberculosis

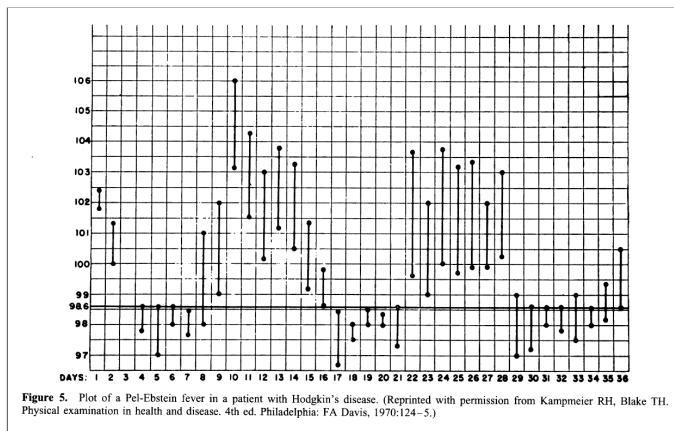


Figure 5. Plot of a Pel-Ebstein fever in a patient with Hodgkin's disease. (Reprinted with permission from Kampmeier RH, Blake TH. Physical examination in health and disease. 4th ed. Philadelphia: FA Davis, 1970:124–5.)

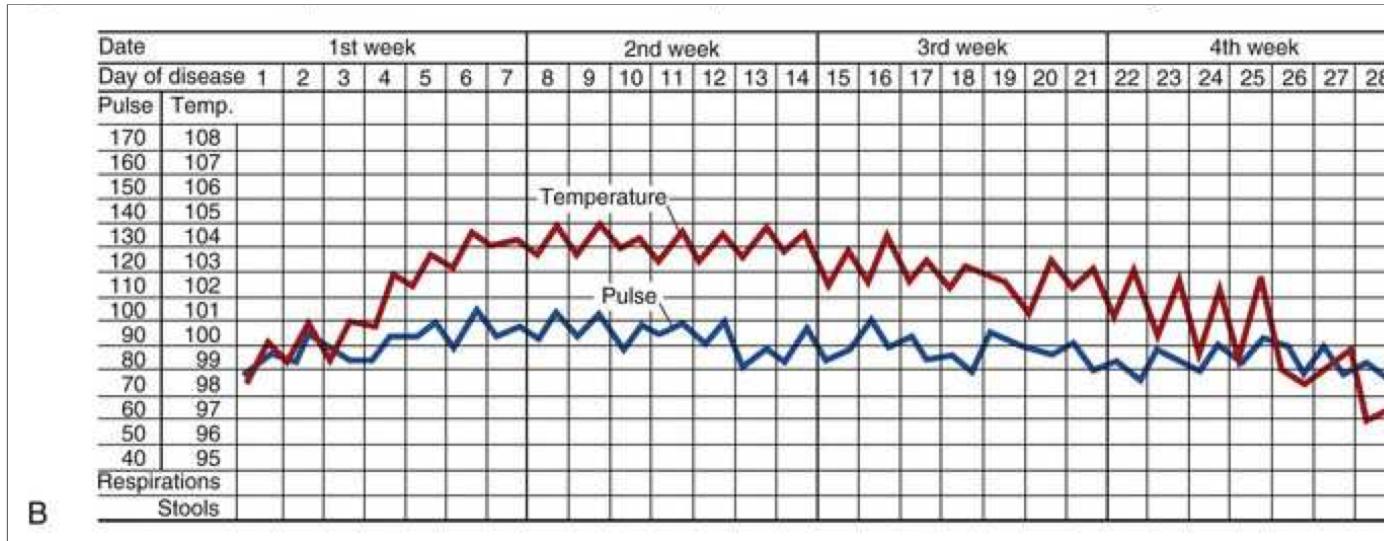
(Mackowiak et al., 1997)

Typus Inversus

- Reversal of diurnal pattern, with highest temperatures in the early morning hours rather than during the late afternoon or evening
 - Miliary TB
 - Salmonelloses
 - Hepatic abscess
 - Bacterial endocarditis

(Mackowiak et al., 1997)

Typhoid fever



Jarisch-Herxheimer reaction

- Sharply increased elevation of temperature with shivers and chills occurs within several hours after starting penicillin therapy
- Lysis of spirochetes
 - Primary or secondary syphilis; Leptospirosis; or tick-borne relapsing fever
 - Tetracycline or chloramphenicol therapy for acute brucellosis

(Mackowiak et al., 1997)

Physical examination

- Some signs are subtle and may require repeated exams to be appreciated
- Vigorous search for lymphadenopathy (consideration for biopsy)

| BODY SITE | PHYSICAL FINDING | DIAGNOSIS |
|-----------------------|---|---|
| Head | Sinus tenderness | Sinusitis |
| Temporal artery | Nodules, reduced pulsations | Temporal arteritis |
| Oropharynx | Ulceration; tender tooth | Disseminated histoplasmosis, periapical abscess |
| Fundi or conjunctivae | Choroid tubercle, petechiae, Roth's spot | Disseminated granulomatosis, [*] endocarditis |
| Thyroid | Enlargement, tenderness | Thyroiditis |
| Heart | Murmur | Infective or marantic endocarditis |
| Abdomen | Enlarged iliac crest lymph nodes, splenomegaly | Lymphoma, [†] endocarditis, disseminated granulomatosis [*] |
| Rectum | Perirectal fluctuance, tenderness | Abscess |
| | Prostatic tenderness, fluctuance | Abscess |
| Genitalia | Testicular nodule | Periarteritis nodosa |
| | Epididymal nodule | Disseminated granulomatosis |
| Lower extremities | Deep venous tenderness | Thrombosis or thrombophlebitis |
| Skin and nails | Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing | Vasculitis, endocarditis |

(Wright, William F. and Mackowiak, Philip A., 2015)

Laboratory investigations

“The cause is more often a *common disease* presenting in an *atypical fashion* than a *rare disease* presenting in a *typical fashion*.

- Multiple diagnostic algorithms in the literature
- Must be selectively applied or will result in excessive unfocused diagnostic testing
 - False positives
 - Misguided treatment plans
- History and physical exam (most important) should guide the choice and sequence of tests

Examples of potential diagnostic clues

| Etiology | Historical Clues | Physical Clues |
|---|--|--|
| Anaplasmosis | Transmitted by the bite of an <i>Ixodes</i> tick in association with outdoor activity in North Central and Eastern United States | Fever, headache, arthralgia, myalgia, pneumonitis, thrombocytopenia, lymphopenia, and elevated liver enzymes |
| Babesiosis | Transmitted by the bite of an <i>Ixodes</i> tick in association with outdoor activity in the Northeastern United States | Arthralgias, myalgias, relative bradycardia, hepatosplenomegaly, anemia, thrombocytopenia, and elevated liver enzymes |
| Bartonellosis | Recent travel to the Andes mountains (<i>Chagas</i> fever; <i>Bartonella bacilliformis</i>), association with homelessness in urban settings (<i>Bartonella quintana</i>) or the scratch of an infected kitten or feral cat (<i>Bartonella henselae</i>) | Conjunctivitis, retro-orbital pain, anterior tibial bone pain, macular rash, nodular plaque lesions, and/or regional lymphadenopathy |
| Blastomycosis | Contact with soil adjacent to the Mississippi and Ohio River valleys, Saint Lawrence River in New York and Canada, and North American Great Lakes or exposure to infected dogs | Arthralgia, atypical pneumonia, pulmonary nodules, and/or fulminant adult respiratory distress syndrome, verrucous, nodular, or ulcerative skin lesions, and prostatitis |
| Brucellosis | Associated with contact or consumption of products from infected goats, pigs, camels, yaks, buffalo, or cows and with abattoir work | Arthralgias, hepatosplenomegaly, suppurative musculoskeletal lesions, sacroiliitis, spondylitis, uveitis, hepatitis, and pancytopenia |
| Coccidioidomycosis | Exposure to soil or dust in the southwestern United States | Arthralgias, pneumonia, pulmonary cavities, pulmonary nodules, erythema multiforme, and erythema nodosum |
| Ehrlichiosis | Transmitted by the bite of an <i>Amblyomma</i> , <i>Dermacentor</i> , or <i>Ixodes</i> tick in association with outdoor activity in midwestern and southeastern United States | Pneumonitis, hepatitis, thrombocytopenia, and lymphopenia |
| Enteric fever (<i>Salmonella enterica</i> serovar <i>Typhi</i>) | Recent travel to a Third World country with consumption of potentially contaminated food or water | Headache, arthritis, abdominal pain, relative bradycardia, hepatosplenomegaly, and leukopenia |
| Histoplasmosis | Exposure to bat or black bird excreta in roosts, chicken houses, or caves in the region surrounding the Ohio and Mississippi River valleys | Headache, pneumonia, pulmonary cavities, mucosal ulcers, adenopathy, erythema nodosum, erythema multiforme, hepatitis, anemia, leukopenia, and thrombocytopenia |
| Leptospirosis | Occupational exposure among workers in sewers, rice and sugar cane fields, and abattoirs. Recreational water sports and exposure to contaminated waters or infected dogs. | Bitemporal and frontal headache, calf and lumbar muscle tenderness, conjunctival suffusion, hepatic and renal failure, and hemorrhagic pneumonitis |
| Leishmaniasis (visceral disease) | Associated with recent travel to areas endemic for sand flies | Hepatosplenomegaly, lymphadenopathy, and hyperpigmentation of the face, hand, foot, and/or abdominal skin (kala azar) |
| Malaria | Recent travel to endemic areas in Asia, Africa, and Central/South America | Fever, headaches, nausea, emesis, diarrhea, hepatomegaly, splenomegaly, and anemia |
| Pittacosis (<i>Chlamydia psittaci</i>) | Associated with contact with birds, especially pittacine birds | Fever, pharyngitis, hepatosplenomegaly, pneumonia, blanching maculopapular eruptions, erythema multiforme, erythema marginatum, and erythema nodosum |
| Q fever (<i>Coxiella burnetii</i>) | Associated with farm, veterinary, or abattoir work; consumption of unpasteurized milk; and contact with infected sheep, goats, or cattle | Atypical pneumonia, hepatitis, hepatomegaly, relative bradycardia, and/or splenomegaly |
| Rat-bite fever (<i>Streptobacillus moniliformis</i>) | Recent bite or scratch by a rat, mice or squirrel and/or ingestion of food or water contaminated by rat excrement | Headaches, myalgias, polyarthritides, and maculopapular, morbilliform, petechial, vesicular, or pustular rash over the palms, soles, and extremities |
| Relapsing fever (<i>Borrelia recurrentis</i>) | Associated with poverty, crowding, and poor sanitation (louse-borne), or with camping (tick-borne), particularly in the Grand Canyon | High fever with rigors, headache, delirium, arthralgias, myalgias, and hepatosplenomegaly |
| Rocky Mountain spotted fever | Associated with outdoor activity in the South Atlantic or southeastern United States and exposure to <i>Dermacentor</i> tick bites | Headache, petechial rash involving the extremities, hand palms, and feet soles |
| Tuberculosis | Recent contact with tuberculosis, recent immigration from an endemic country, and work or residence in homeless shelters, correctional facilities or health care facilities | Night sweats, weight loss, atypical pneumonia, cavitary pulmonary lesions |
| Tularemia | Associated with bites by <i>Amblyomma</i> or <i>Dermacentor</i> ticks, deer flies, and mosquitoes or direct contact with the tissues of infected animals such as rabbits, squirrels, deer, raccoons, cattle, sheep, and swine | Ulceraic skin lesions at a bite site, pneumonia, relative bradycardia, lymphadenopathy, and conjunctivitis |
| Whipple's disease (<i>Tropheryma whipplei</i>) | Potential association with exposure to sewage | Chronic diarrhea, arthralgia, weight loss, malabsorption, and malnutrition |

(Wright, William F. and Mackowiak, Philip A., 2015)

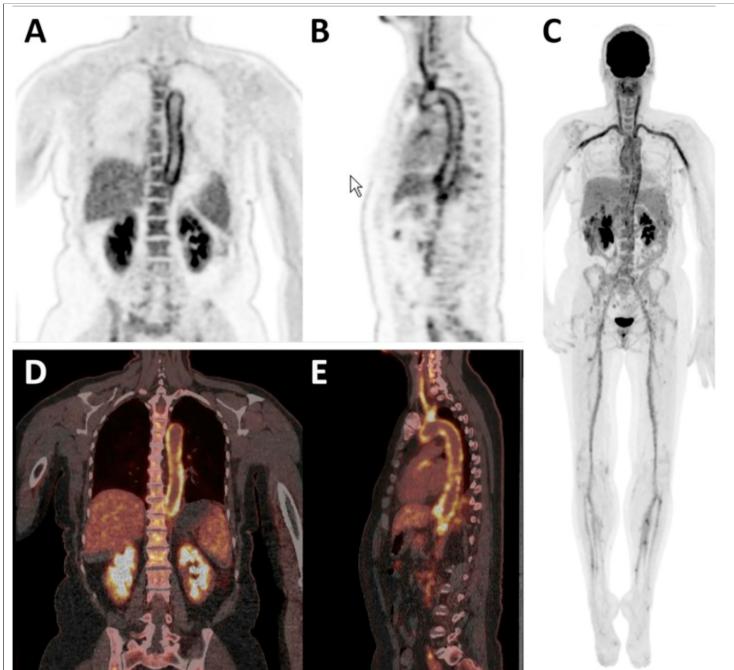
Bone marrow biopsy

- Granulomatous infections (e.g., tuberculosis, histoplasmosis, sarcoidosis)
- Patients with abnormal complete blood counts (CBC)

Imaging studies

- Generally low diagnostic yield without localizing symptoms
 - CT of abdomen, chest
 - Ultrasound of gallbladder and hepatobiliary systems
 - CT pulmonary angiograms for pulmonary embolus
 - MRI for CNS, abdomen spleen and lymph nodes Aortic arch and proximal cervical arteries (vasculitis)
 - The indium 111- tagged white blood cell (WBC) scan (becoming less common)
 - Gallium-67 (^{67}Ga) scan (replaced by PET-CT)

¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET)



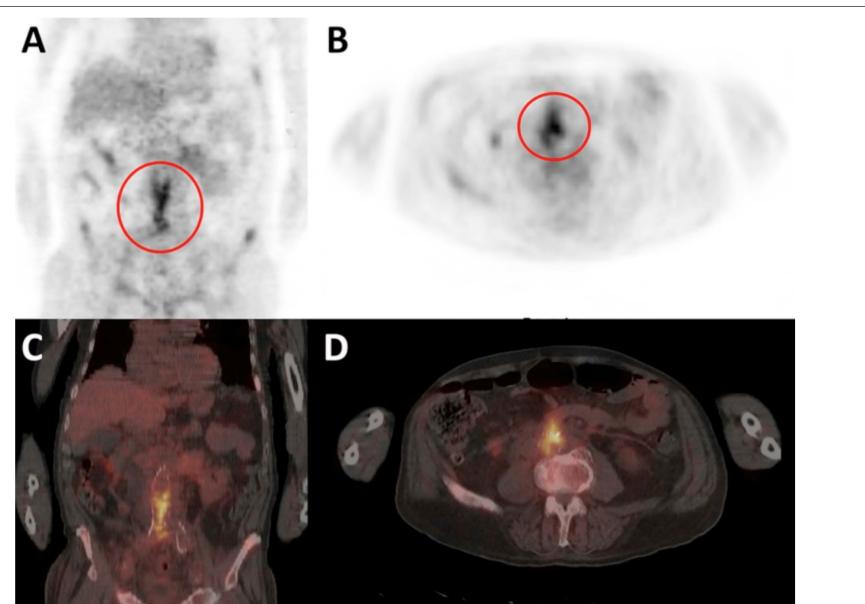
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Figure 1. A 60-year-old woman presented with fever, night sweats, and arthralgia. Physical examination was normal. ESR was 125 mm/hour and leukocyte count was $12.4 \times 10^9/L$ with normal creatinine level and liver function tests. FDG-PET/CT showed highly increased FDG uptake of the aorta, subclavian arteries, and femoral arteries. Patient was diagnosed with large vessel vasculitis. Her symptoms resolved and ESR normalized upon treatment with corticosteroids.

(de Kleijn et al., 1997; Wright et al., 2021)

F-fluorodeoxyglucose (FDG) positron emission tomography (PET)



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Figure 2. A 75-year-old man, with a medical history of an aortic vascular prosthesis due to a symptomatic aneurysm and metastatic prostate carcinoma, presented with fever and night sweats. Physical examination was normal. CRP was 130 mg/L and leukocyte count was $11.0 \times 10^9/\text{L}$ with normal creatinine level but increased AF (220 U/L) and LDH (771 U/L). FDG-PET/CT depicted beside the known metastatic prostate carcinoma infection of the aortic graft. Blood cultures were positive for Streptococcus anginosus, and the patient was treated with amoxicillin and clavulanic acid until his death 6 months later.

(Kouijzer et al., 2018)

Invasive diagnostic procedures

- Histopathological examination of tissues obtained by excisional biopsy , needle biopsy or laparotomy can provide definitive diagnosis in some cases
- Majority of FUO patients will undergo at least one procedure

Treatment

- A fundamental principle in classic FUO is that therapy should be withheld until the cause of fever is determined
 - Non-specific treatment rarely “cures” FUO
 - Empiric treatment may delay the clinical diagnosis
- Clinical reality is that therapeutic trials with corticosteroids, aspirin, antimicrobial agents may be considered
 - May delay correct diagnosis/treatment
 - The road to diagnosis of FUO is, by definition, long and frustrating
 - Clinicians are often pressured to treat symptoms
 -

Diagnostic summary

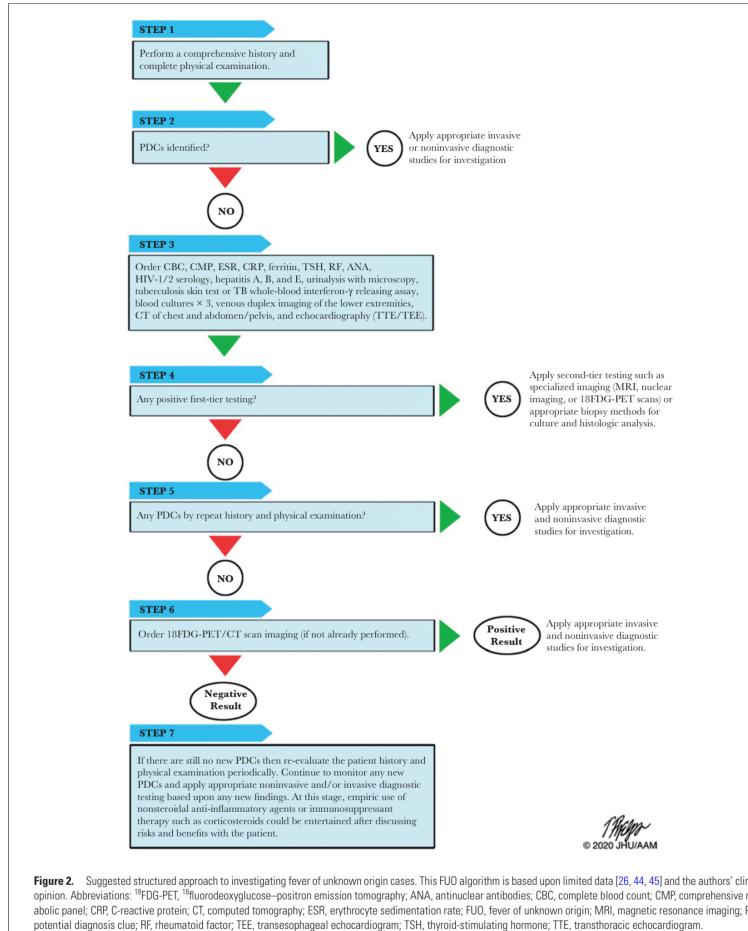


Figure 2. Suggested structured approach to investigating fever of unknown origin cases. This FUO algorithm is based upon limited data [26, 44, 45] and the authors' clinical opinion. Abbreviations: $^{18}\text{FDG-PET}$, ^{18}F fluorodeoxyglucose–positron emission tomography; ANA, antinuclear antibodies; CBC, complete blood count; CMP, comprehensive metabolic panel; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FUO, fever of unknown origin; MRI, magnetic resonance imaging; PDC, potential diagnosis clue; RF, rheumatoid factor; TEE, transesophageal echocardiogram; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram.

(Wright and Auwaerter, 2020)

When is immediate treatment indicated?

- Empirical treatment with corticosteroids in patients with **suspected temporal arteritis** to prevent vascular complications such as blindness and stroke
- **Febrile neutropenia or other severely immunocompromised patients:** high prevalence of serious bacterial infections- patients should receive broad-spectrum antimicrobial therapy with anti-pseudomonas coverage after appropriate cultures are obtained
- Therapeutic trials with narrow spectrum therapy (e.g. anti-mycobacterial agents) may be considered in select cases with history suggestive of TB

Prognosis

- Determined by the cause of fever and nature of underlying disease(s)
- Elderly patients with malignant neoplasms have the poorest prognosis
- Diagnostic delay associated with poorer prognosis in:
 - Intra-abdominal infections
 - Miliary tuberculosis
 - Disseminated fungal infections
 - Recurrent pulmonary emboli
- Patients with undiagnosed FUO after extensive evaluation still generally have a favourable outcome, with most patients experiencing resolution of fever within 4 weeks without sequelae.
 - 5-year mortality rates of 3%

References

- Corey L, Boeckh M. Persistent fever in patients with neutropenia. *The New England Journal of Medicine* 2002;346:222–4. <https://doi.org/10.1056/NEJM200201243460402>.
- de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. Prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. *The Netherlands FUO Study Group. Medicine* 1997;76:392–400. <https://doi.org/10.1097/00005792-199711000-00002>.
- Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *The New England Journal of Medicine* 1999;340:448–54.
<https://doi.org/10.1056/NEJM199902113400607>.
- Haidar G, Singh N. Fever of Unknown Origin. *New England Journal of Medicine* 2022;386:463–77. <https://doi.org/10.1056/NEJMra2111003>.
- Kouijzer IJE, Mulders-Manders CM, Bleeker-Rovers CP, Oyen WJG. Fever of Unknown Origin: The Value of FDG-PET/CT. *Seminars in Nuclear Medicine* 2018;48:100–7.
<https://doi.org/10.1053/j.semnuclmed.2017.11.004>.
- Mackowiak PA, Bartlett JG, Borden EC, Goldblum SE, Hasday JD, Munford RS, et al. **Concepts of Fever: Recent Advances and Lingering Dogma.** *Clinical Infectious Diseases* 1997;25:119–38.
- Mackowiak PA, Worden G. Carl Reinhold August Wunderlich and the evolution of clinical thermometry. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 1994;18:458–67. <https://doi.org/10.1093/clinids/18.3.458>.
- Playfair, J., Bancroft, G. *Infection and Immunity*, 4th Edition. Oxford University Press; 2013.
- Sajadi, Mohammad M., Mackowiak, Philip A. Temperature Regulation and the Pathogenesis of Fever. *Principles and Practice of Infectious Diseases*, 8th Edition, Elsevier Health Sciences; n.d., p. 4739–452.
- Sickles EA, Greene WH, Wiernik PH. **Clinical presentation of infection in granulocytopenic patients.** *Archives of Internal Medicine* 1975;135:715–9.
- Wright WF, Auwaerter PG. Fever and Fever of Unknown Origin: Review, Recent Advances, and Lingering Dogma. *Open Forum Infectious Diseases* 2020;7:ofaa132.
<https://doi.org/10.1093/ofid/ofaa132>.
- Wright WF, Auwaerter PG, Dibble EH, Rowe SP, Mackowiak PA. Imaging a Fever-Redefining the Role of 2-deoxy-2-[18F]Fluoro-D-Glucose-Positron Emission Tomography/Computed Tomography in Fever of Unknown Origin Investigations. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 2021;72:1279–86. <https://doi.org/10.1093/cid/ciaa1220>.
- Wright, William F., Mackowiak, Philip A. *Principles and Practice of Infectious Diseases*, 8th Edition. Fever of Unknown Origin, Elsevier Health Sciences; 2015.