Fever of Unknown Origin (FUO)

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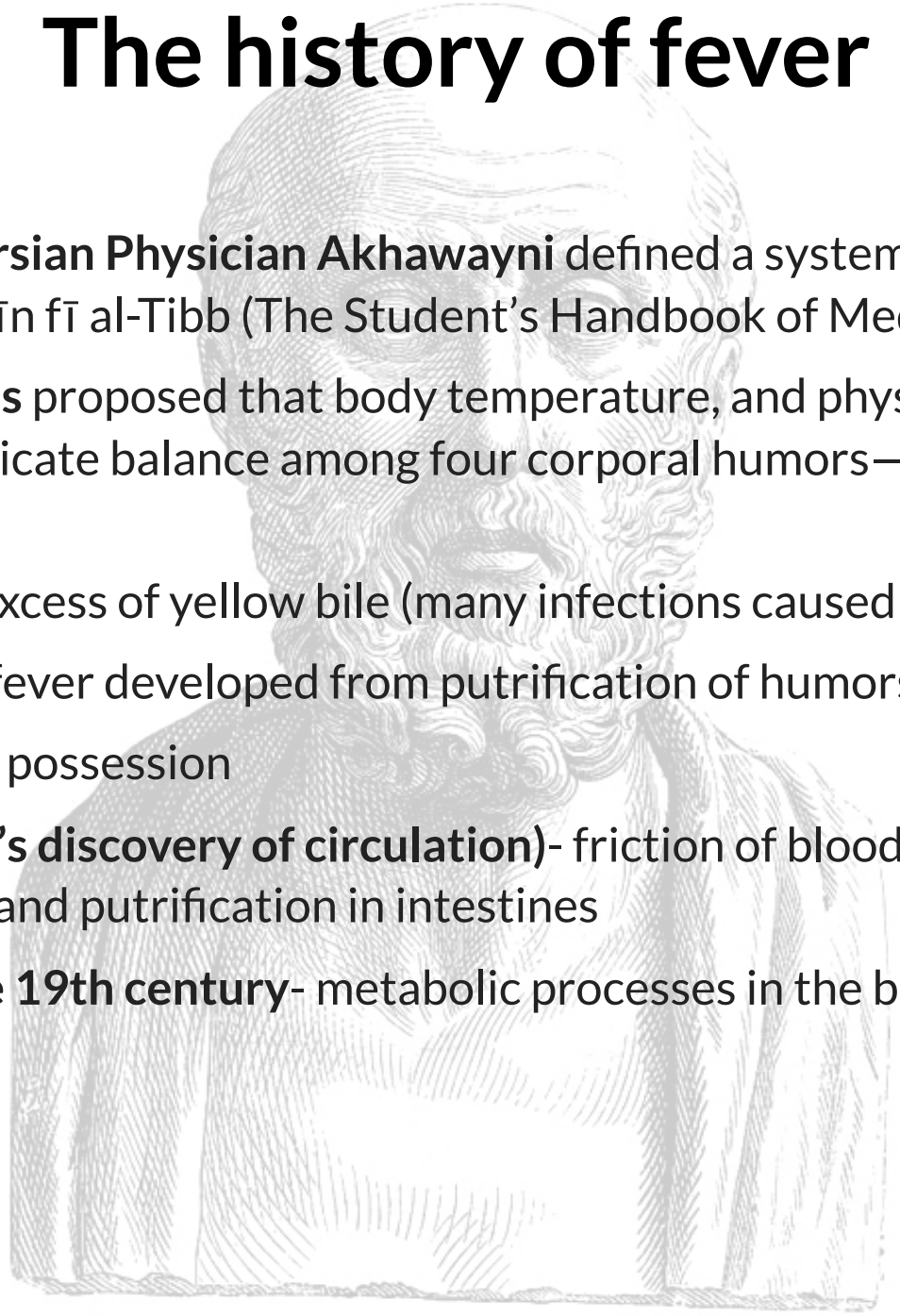
Università
degli Studi
di Padova

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 spectum of pathogens in immunocompromised hosts

The history of fever

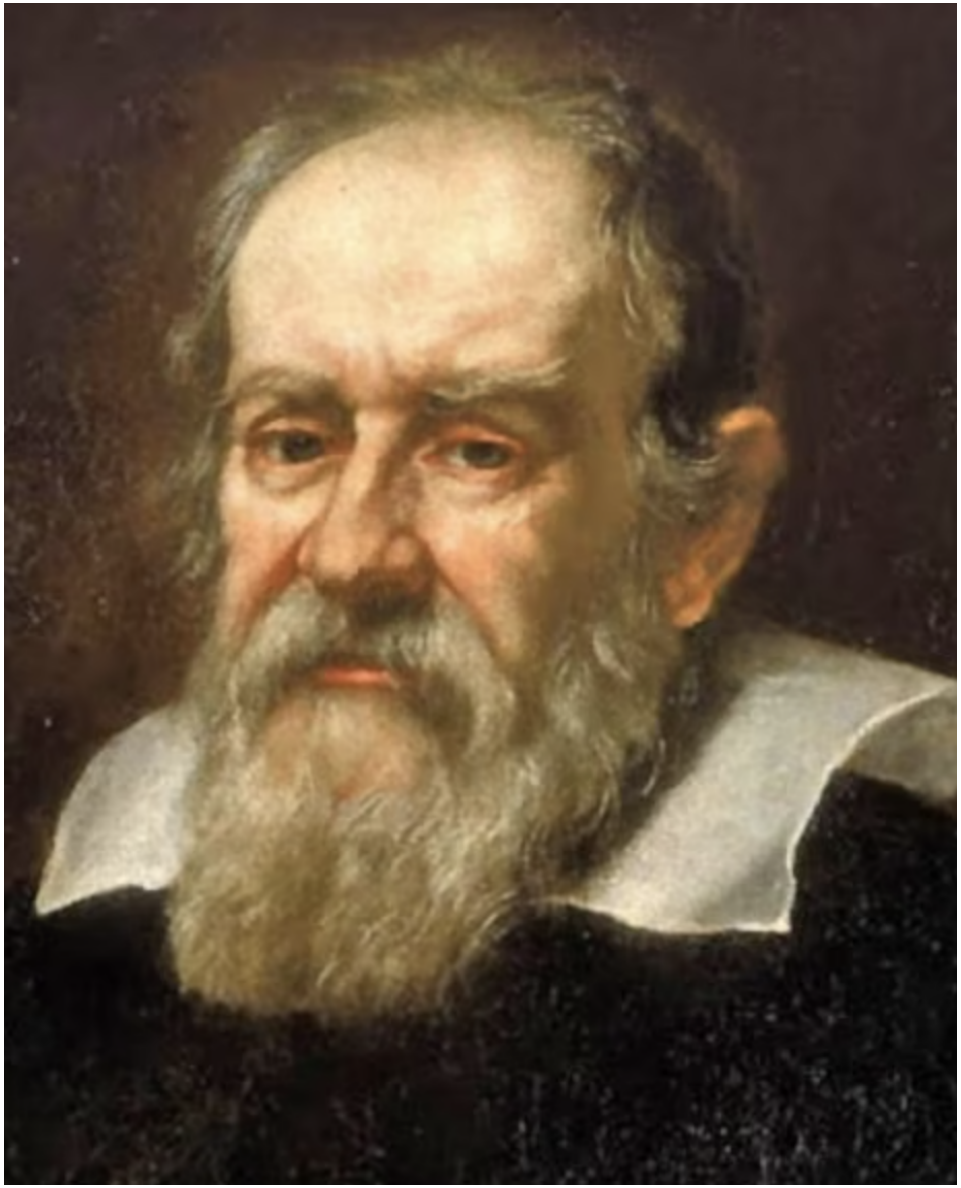


- **10th Century BCE Persian Physician Akhawayni** defined a system for fever curves in Hidāyat al-Muta'allimīn fī al-Tibb (The Student's Handbook of Medicine)
- **Hippocratic physicians** proposed that body temperature, and physiologic harmony in general, involved a delicate balance among four corporal 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



Scorri sopra l'immagine per ingrandirla

TERMOMETRO GALILEO Tubo di vetro 44 cm, per esterni o interni, analogici, sfere galleggianti

Marca: Signes Grimalt

4,5 stelle 33 voti

73,80 €

Tutti i prezzi includono l'IVA.

Promozioni Acquista 2, risparmia 5€ 1 promozione

Marchio	Signes Grimalt
Colore	Trasparente
Conteggio unità	1.0 unità
Lunghezza articolo	43 cm

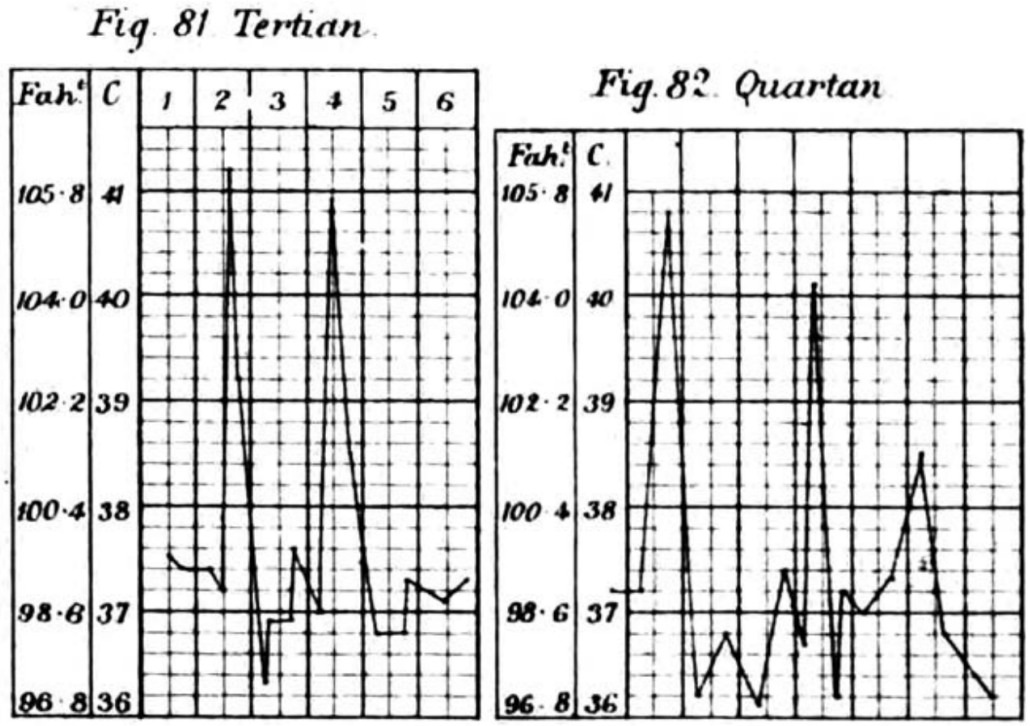
Valutazione (sui prodotti da parte dell'acquirente) per caratteristica

Stile	4,5
Ottimo rapporto qualità-prezzo	4,4

Visualizza tutte le recensioni

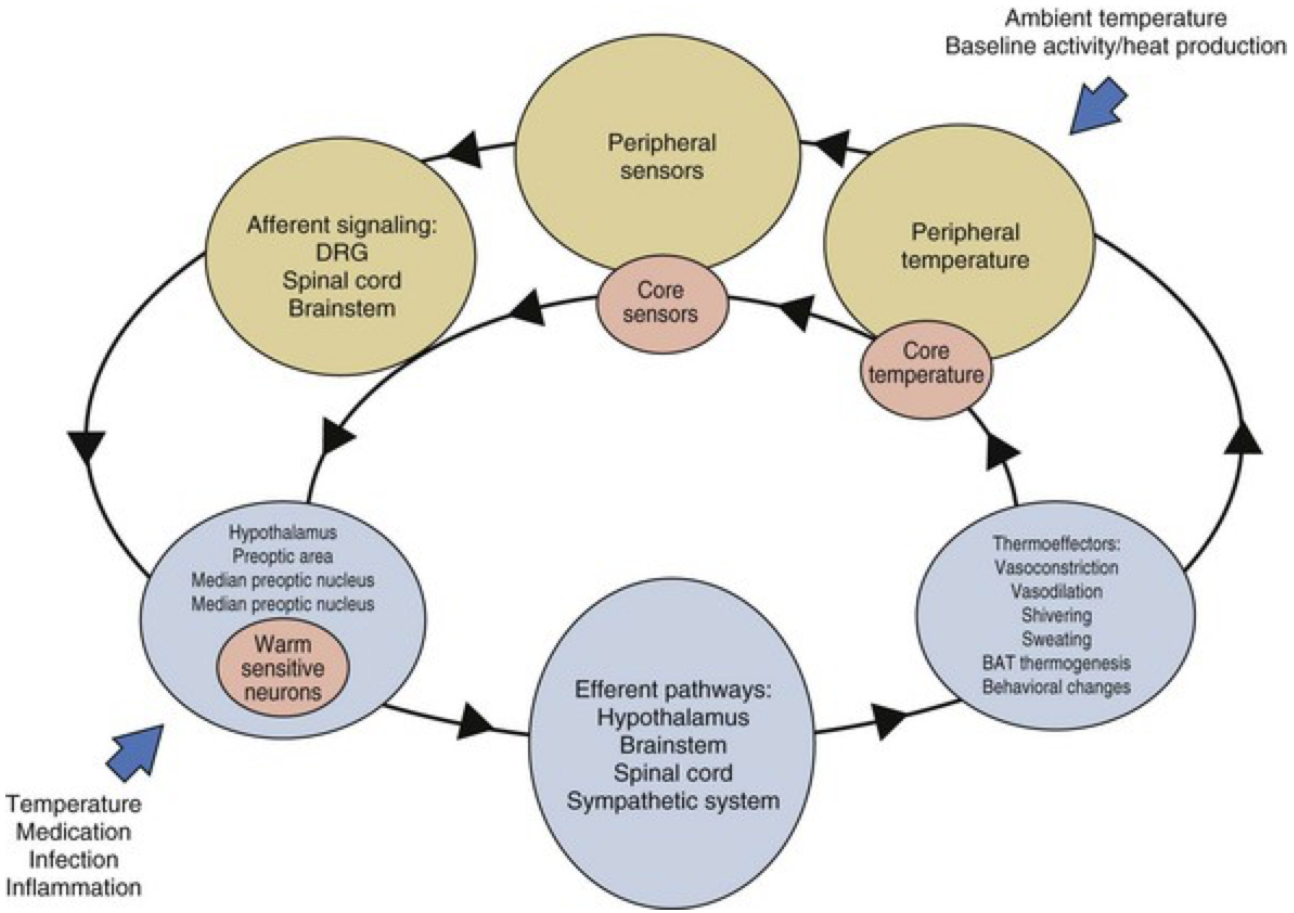
Fever in modern medicine

- 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



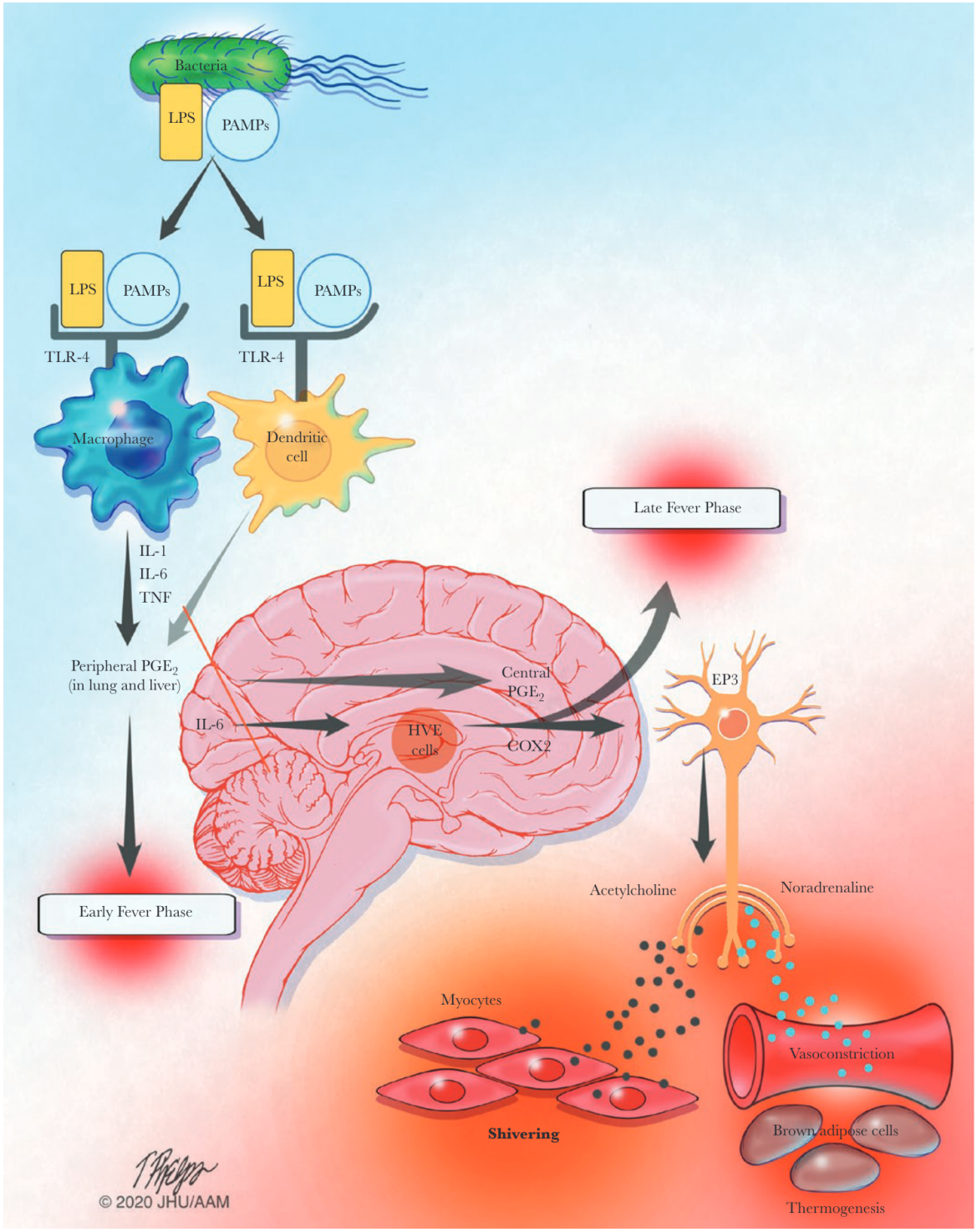
(Mackowiak and Worden, 1994)

Thermal homeostasis



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

Infection-associated fever


Bacteria
LPS
PAMPs
LPS
PAMPs
LPS
PAMPs
TLR-4
TLR-4
Macrophage
Dendritic cell
IL-1
IL-6
TNF
Late Fever Phase
Peripheral PGE_2 (in lung and liver)
Central PGE_2
EP3
IL-6
HVE cells
COX2
Early Fever Phase
Acetylcholine
Noradrenaline
Myocytes
Vasoconstriction
Shivering
Brown adipose cells
Thermogenesis
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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 the bind free iron necessary for microbial replication

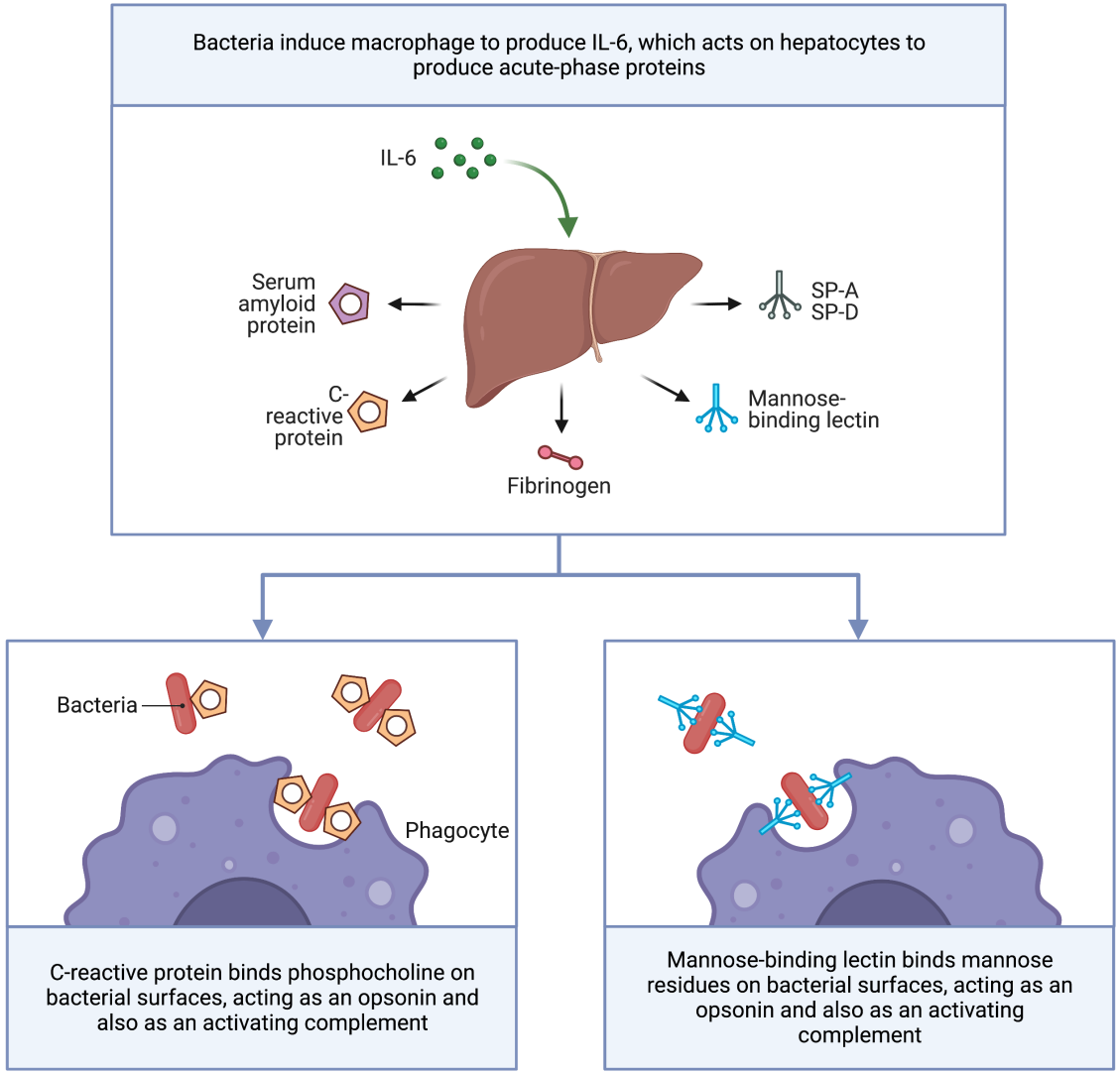
Acute phase proteins

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, hypoferremia, 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, *Clostridioides difficile* 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, *Strongyloides stercoralis* 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 Street[3] 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°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

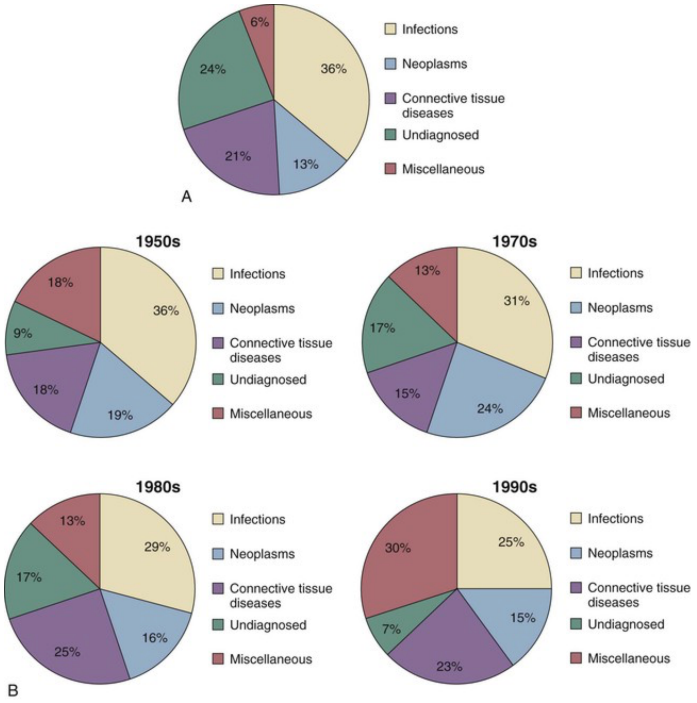


FIGURE 56-1 **A,** Frequency of the five main etiologic categories of fever of unknown origin. **B,** Frequency of the five main etiologic categories of fever of unknown origin by decade. (**A** from Hayakawa K, et al. Fever of unknown origin: an evidence-based review. *Am J Med Sci.* 2012;344:307-316; **B** from Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med.* 2003;163:545-551.)

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

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/mm^3 or an ANC that is expected to decrease to < 500 cells/mm^3 during the next 48 h.
  - The term “profound” is sometimes used to describe neutropenia in which the ANC is < 100 cells/mm^3
- 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)

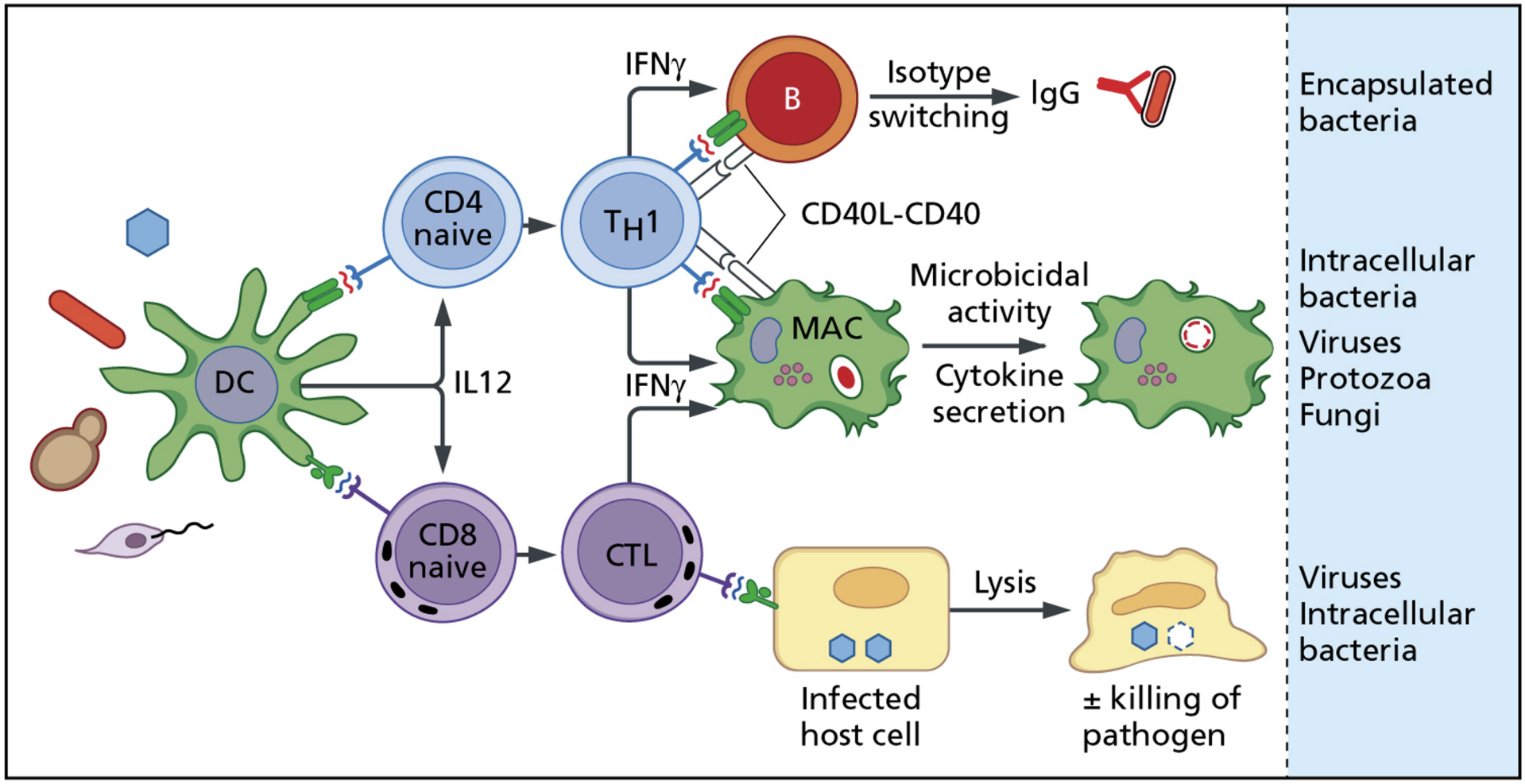
Signs and symptoms	Infection	% of patients with ANC< 100	% of patients with ANC>1000
Fever	Overall	98	76
Bacteremia	Overall	43	13
Fluctuance	Anorectal	8	67
Exudate	Skin	5	92
Purulent sputum	Pneumonia	8	84
Pyuria	UTI	11	97

(Sickles et al., 1975)

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

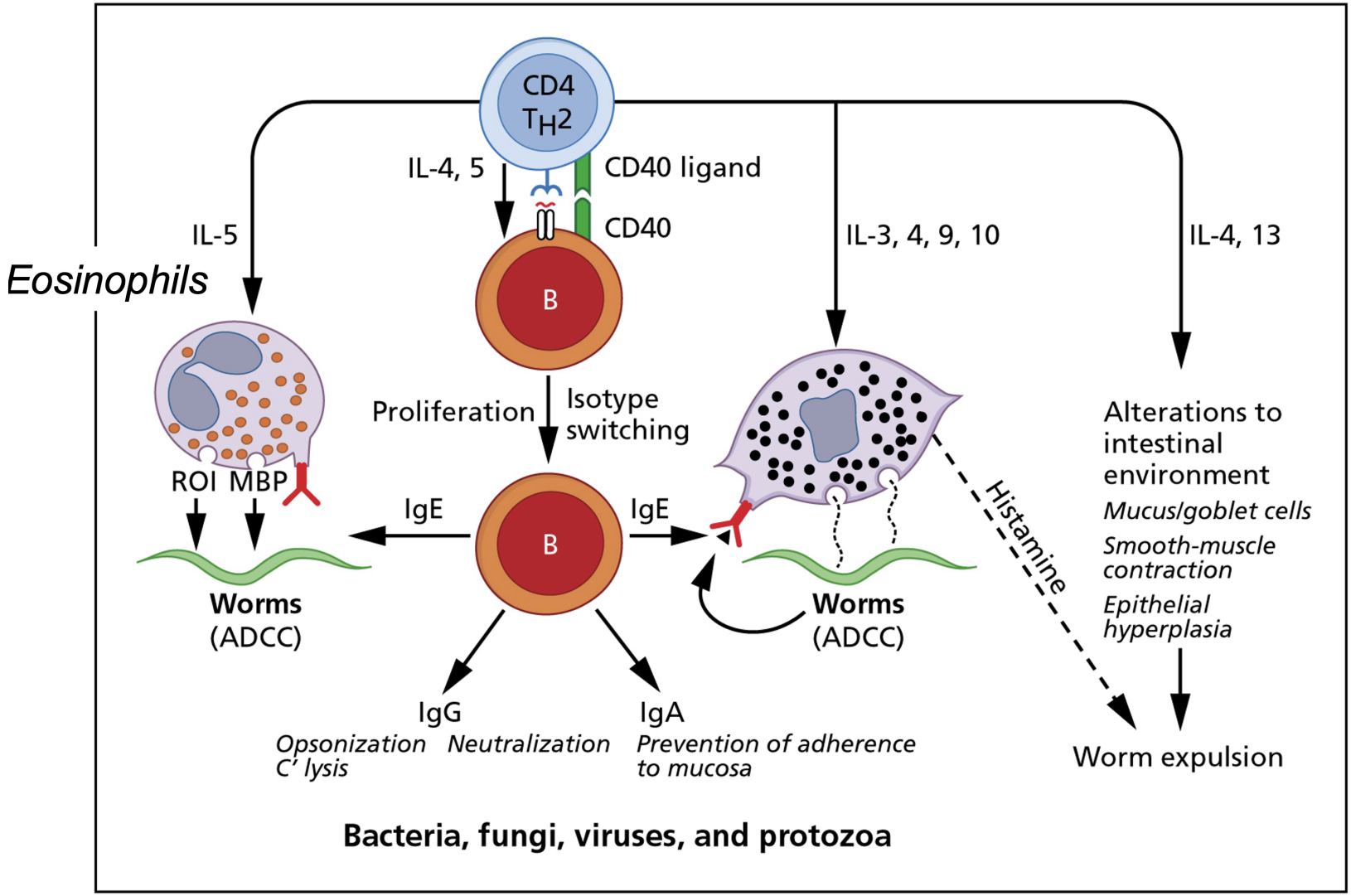
CAUSES	APPROXIMATE FREQUENCY IN HIGH-RISK PATIENTS (%)
Fungal infections susceptible to empirical therapy	40
Fungal infections resistant to empirical antifungal therapy	5
Bacterial infections (with cryptic foci, biofilms, and resistant organisms)	10
Toxoplasma gondii, mycobacteria, or fastidious pathogens *(Legionella, Mycoplasma, Chlamydia pneumoniae, Bartonella)*	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

Cell-mediated immunity-1



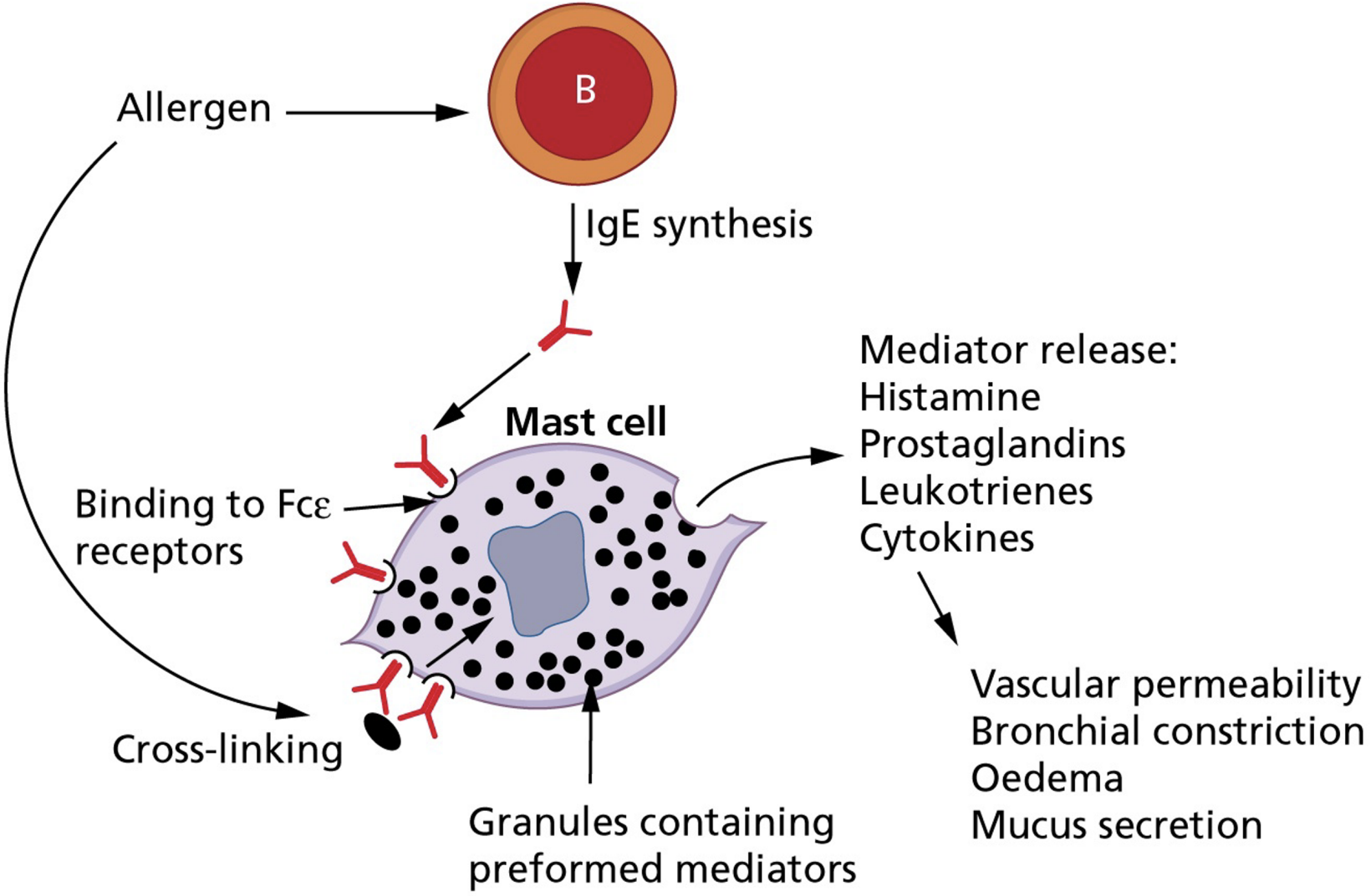
(Playfair, J. and Bancroft, G., 2013)

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

Infections in Immunocompromised Hosts

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(*All contributed equally)

Innate Immunity

Neutrophils, macrophages, monocytes, dendritic cells, NK cells, complement

Neutropenia

Hematologic malignancies, chemotherapy, medication-induced, cyclic neutropenia, congenital neutropenias
- Bacterial → enteric/pseudomonal immediately after cytotoxic chemo
- Viral (HSV, VZV)
- Prolonged (3-4 weeks) → molds (Aspergillus, Mucorales spp, etc)

Phagocytic Deficiencies

Chronic granulomatous disease, Leukocyte adhesion deficiency
- Bacterial: Staph, Nocardia, Serratia, Burkholderia
- Fungal: Candida, Aspergillus

Complement Deficiency

Hereditary/acquired deficiency
Encapsulated bacteria (Neisseria, Strep pneumo, H. flu, Klebsiella)

Anti-complement therapy ex. Eculizumab
>1000 x Increased risk of invasive meningococcal disease (requires Ppx and vaccination)

Both

Solid Organ Transplant

Risk associated with NET STATE of immunosuppression: time since transplant, recent episode of rejection, current immunosuppressive regimen

<1 month
- Donor-derived infections
- Hospital-acquired infections (MRSA, VRE, PSA); CRBSI, CAUTI, wound infection, C.diff; Candida

1-6 months (up to 12 mo)
(Ppx Bactrim +/-CMV Ppx)
- Off ppx: PJP, toxoplasmosis, CMV, VZV, HSV, Hep B, Nocardia, Strongyloides
- On ppx: BK (kidney), C.diff, adenovirus, flu, endemic mycoses, Strongyloides

>6-12 months (If no recent change to immunosuppression or rejection)
- Community acquired PNA, UTI, SSTI
- Long term: EBV → PTLD, HSV/CMV, Nocardia

Allogeneic Stem Cell Transplant

Risk associated with time since transplant, presence/severity of GVHD, and current immunosuppressive regimen

<1 month
Neutropenia
Viral: Respiratory and Enteric, HSV, HHV-6
Bacterial: Gram-negative, Staph epi, viridians group Strep
Fungal: Candida, Aspergillus, Mucorales spp

~1-3 months
Cell-mediated immunity compromised
Viral: Respiratory and Enteric, BK virus, CMV, HSV, HHV-6, EBV, disseminated adenovirus
Bacterial: Staph epi
Fungal: Candida, Aspergillus, PJP, Toxo

>3 months
Cell-mediated & Humoral immunity compromised
Viral: CMV, HHV-6, EBV, VZV, HSV
Bacterial: Encapsulated organisms
Fungal: Aspergillus, PJP

Medications

Steroids (dose- and duration-dependent)
Generalized increased risk of infection
(Ppx Bactrim if ≥20 mg/day for ≥3 weeks)
- Candida, VZV, TB, PJP, molds, Strongyloides

TNF-alpha inhibitors
- TB, Endemic mycoses (Histo>Cocci>>Blasto)
- HCV, HBV reactivation
- Increased risk of Listeria, Legionella, septic arthritis

Chronic Diseases

CKD/ESRD: PNA, UTI, severe Influenza, line infections (risk: CVC/PDA catheter > graft > fistula)
Cirrhosis: SBP (pneumococcus, enterics), Cryptococcus, "water" bugs: Vibrio, Aeromonas, Pleisiomonas, Edwardsiella
Diabetes: Polymicrobial wound infections, ENT infections, Candida, Mucorales spp (esp poorly controlled/DKA)

Adaptive Immunity

Cell-mediated immunity (T cells)

HIV
Overall increased risk of PNA, TB, VZV, Severe Influenza regardless of CD4 level

Major risk associated with CD4 level

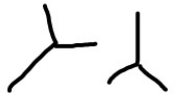
<200 (Ppx Bactrim)
- PJP, Candida

<150
- Histoplasmosis

<100
- Toxoplasmosis (reactivation)
- Cryptococcus

<50 (no longer rec azithromycin)
- MAC (disseminated)
- PML 2/2 JC virus
- CNS lymphoma
- Disseminated CMV/HSV/VZV
- HHV-8-associated disease (KS)
- Bacillary angiomatosis
- Diarrhea: MAC, CMV/HSV, Cryptosporidium, microsporidia, HIV enteropathy

Specific Chemotherapies (ALL therapy, purine analogs (ex fludarabine), alemtuzumab)
Risks similar to HIV



Natalizumab
- Increased risk of PML 2/2 JC virus

Humoral immunity (B cells and antibodies)

CVID, MM, agammaglobulinemia
- Encapsulated organisms (Neisseria, Strep pneumo, H.flu, Klebsiella), Staph aureus
- Sinopulmonary infections
- Capnocytophaga

Anatomic or functional Asplenia
- Same as above
- Babesia
- Bordatella holmesii
- Increased mortality from sepsis

Anti-CD20 monoclonal Ab (Rituximab)
- Hep B reactivation, PML, PJP, Toxo, VZV/HSV

Both (Humoral and cell-mediated)

Severe Combined Immunodeficiency (SCID)
- Intracellular organisms: Viral, fungal

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

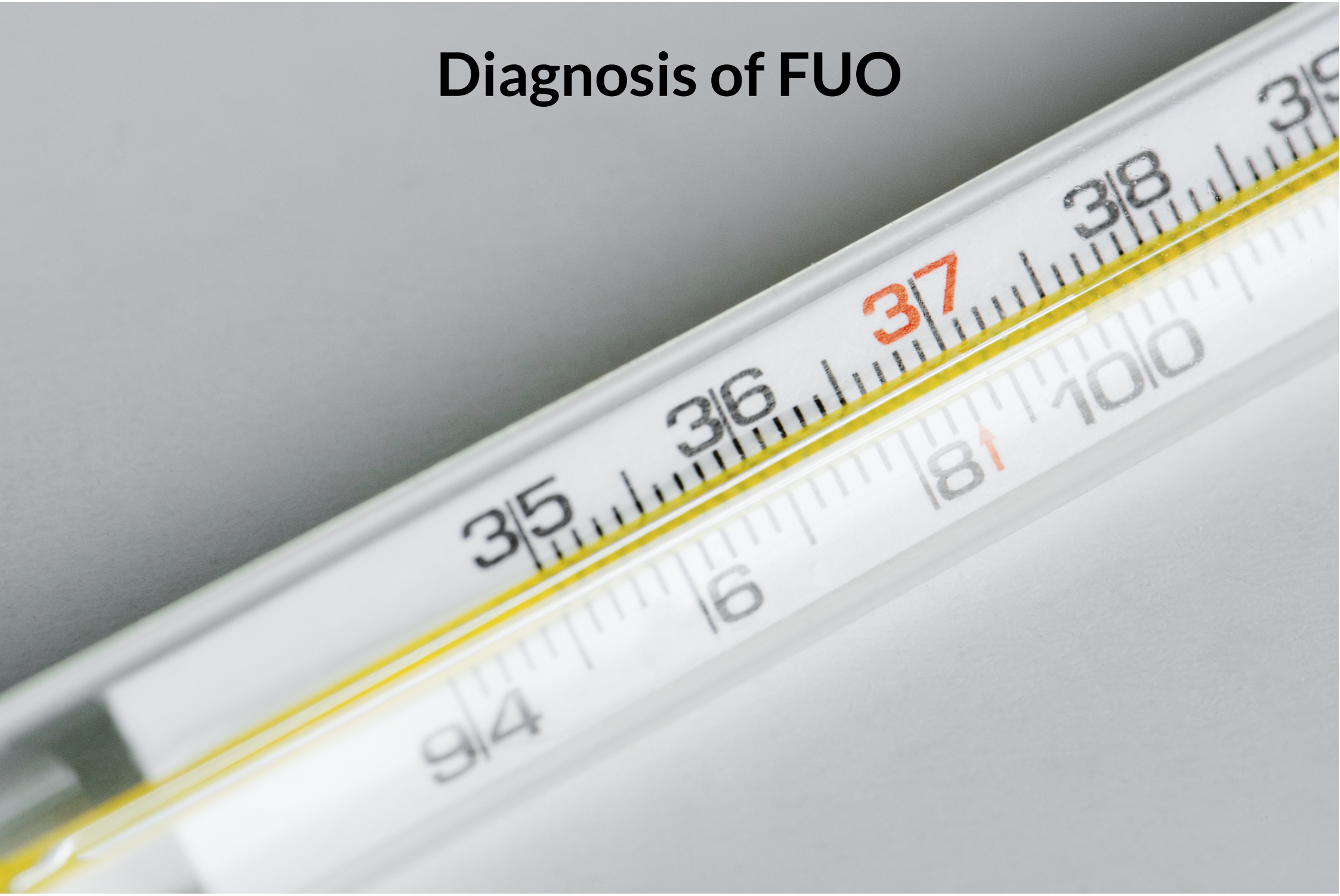
Etiology of fever in HIV-Associated FUO (n=70)

(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°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

Comprehensive history
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

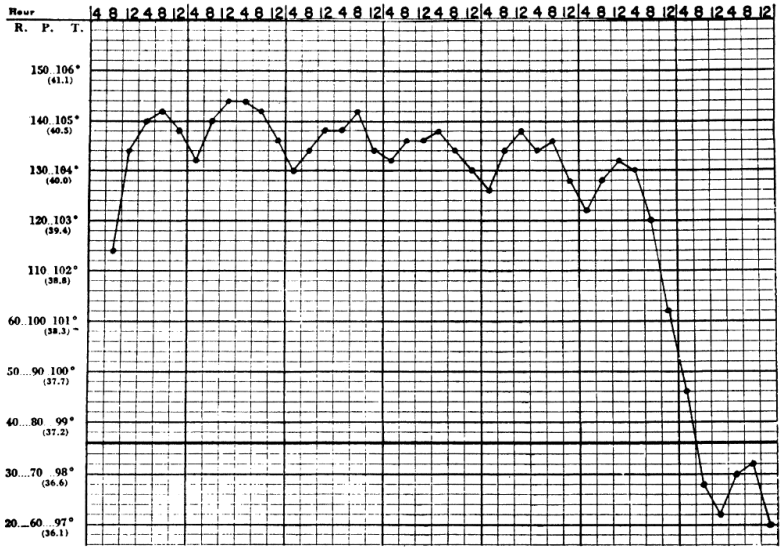
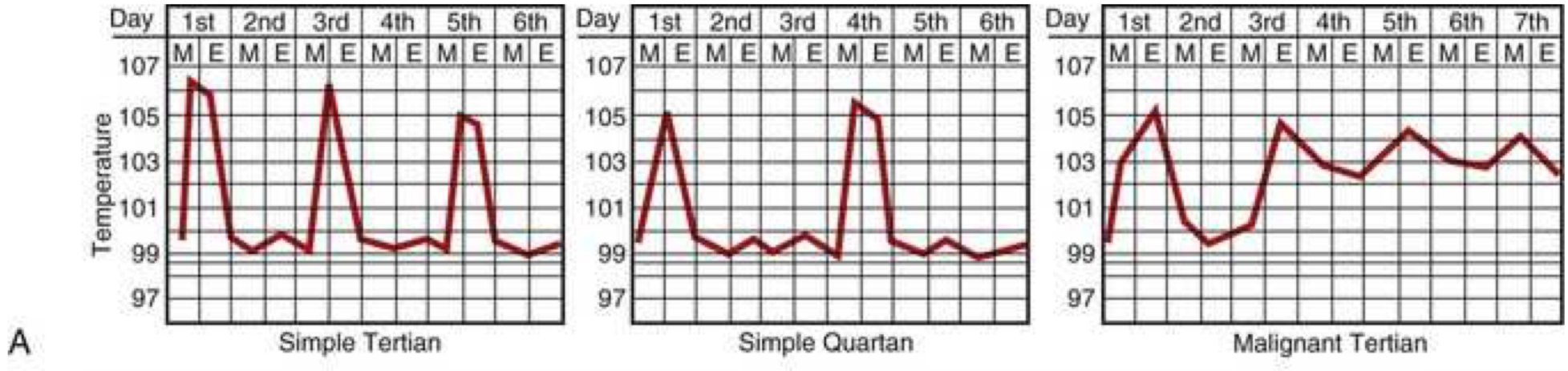


Figure 3. Plot of a continuous fever, ending by crisis, in a patient with lobar pneumonia. (Reprinted with permission from Kampmeier RH, Blake TH. Physical examination in health and disease. 4th ed. Philadelphia: FA Davis, 1970:124–5.)

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 patter (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

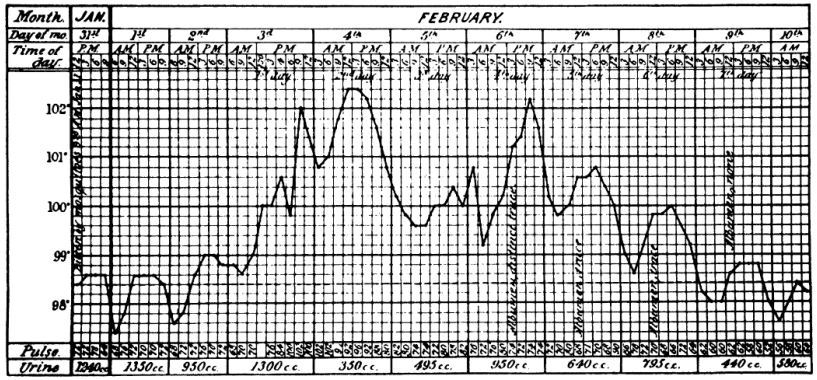


Figure 4. Plot of a saddle-back (biphasic) fever in a patient with yellow fever. (Reprinted from Reed W., et al. Experimental yellow fever. Am Med 1901;III:12.)

(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

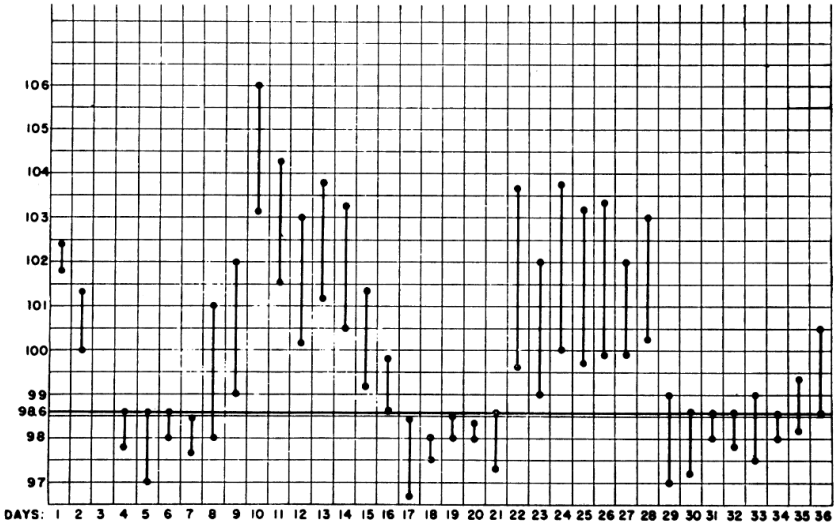


Figure 5. Plot of a Pel-Ebstein fever in a patient with Hodgkin's disease. (Reprinted with permission from Kampmeier RH, Blake TH. Physical examination in health and disease. 4th ed. Philadelphia: FA Davis, 1970:124–5.)

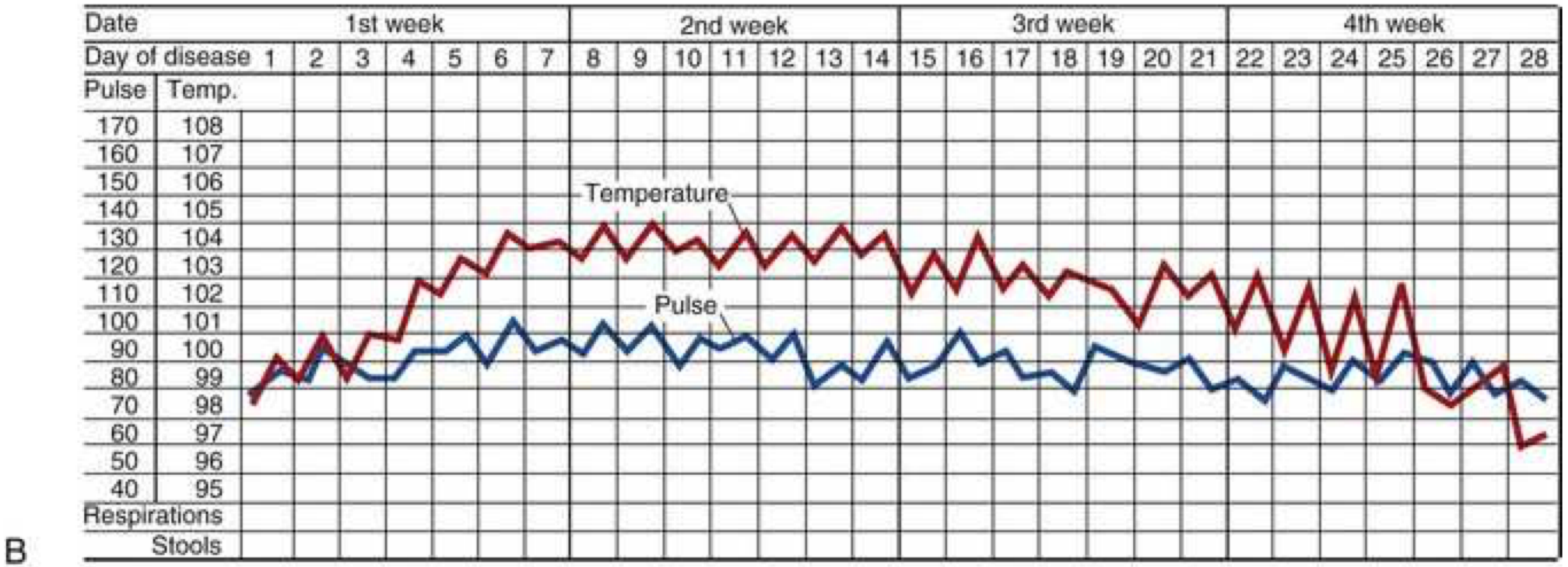
(Mackowiak et al., 1997)

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



B

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 diagnositc 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 *Ixodes* 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 *Ixodes* 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 (Oroya fever; *Bartonella bacilliformis*), association with homelessness in urban settings (*Bartonella quintana*) or the scratch of an infected kitten or feral cat (*Bartonella henselae*)	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	Arthritis, 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 *Amblyomma*, *Dermacentor*, or *Ixodes* tick in association with outdoor activity in midwestern and southeastern United States	Pneumonitis, hepatitis, thrombocytopenia, and lymphopenia
Enteric fever (*Salmonella enterica* serovar Typhi)	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
Psittacosis (*Chlamydia psittaci*)	Associated with contact with birds, especially psittacine birds	Fever, pharyngitis, hepatosplenomegaly, pneumonia, blanching maculopapular eruptions, erythema multiforme, erythema marginatum, and erythema nodosum
Q fever (*Coxiella burnetii*)	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 (*Streptobacillus moniliformis*)	Recent bite or scratch by a rat, mice or squirrel and/or ingestion of food or water contaminated by rat excrement	Headaches, myalgias, polyarthritis, and maculopapular, morbilliform, petechial, vesicular, or pustular rash over the palms, soles, and extremities
Relapsing fever (*Borrelia recurrentis*)	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 *Dermacentor* 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 *Amblyomma* or *Dermacentor* ticks, deer flies, and mosquitoes or direct contact with the tissues of infected animals such as rabbits, squirrels, deer, raccoons, cattle, sheep, and swine	Ulcerated skin lesions at a bite site, pneumonia, relative bradycardia, lymphadenopathy, and conjunctivitis
Whipple's disease (*Tropheryma whippelii*)	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 comon)
  - Gallium-67 (^{67}Ga) scan (replaced by PET-CT)

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)

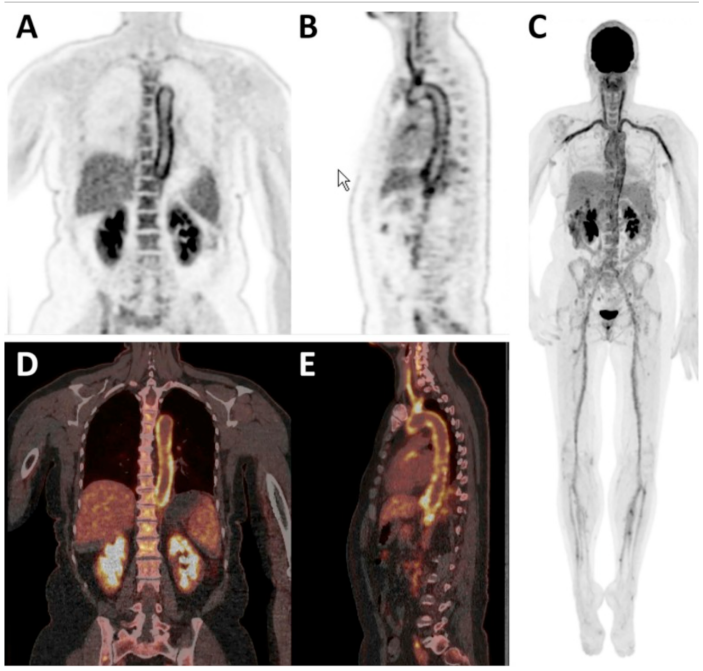


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Figure 1. A 60-year-old woman presented with fever, night sweats, and arthralgia. Physical examination was normal. ESR was 125 mm/hour and leukocyte count was 12.4 × 10^9/L with normal creatinine level and liver function tests. FDG-PET/CT showed highly 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)

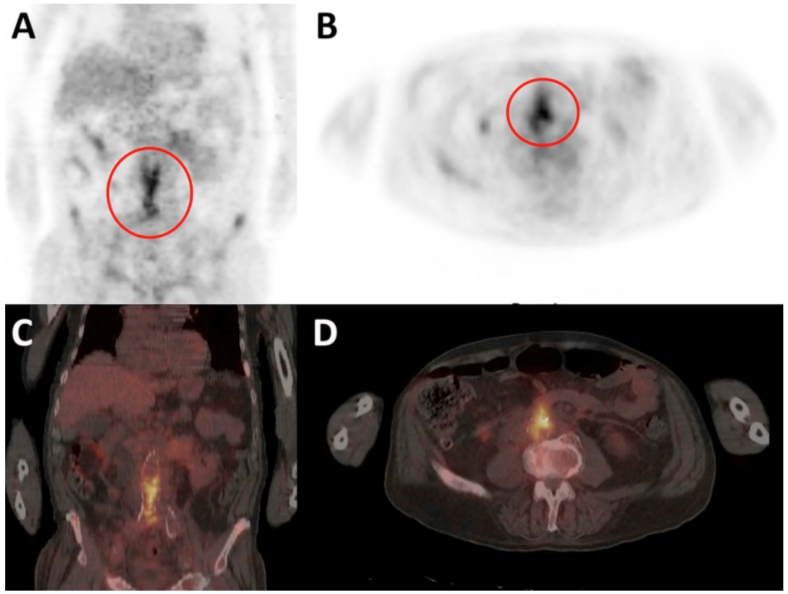

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Figure 2. A 75-year-old man, with a medical history of an aortic vascular prosthesis due to a symptomatic aneurysm and metastatic prostate carcinoma, presented with fever and night sweats. Physical examination was normal. CRP was 130 mg/L and leukocyte count was 11.0×10^9/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

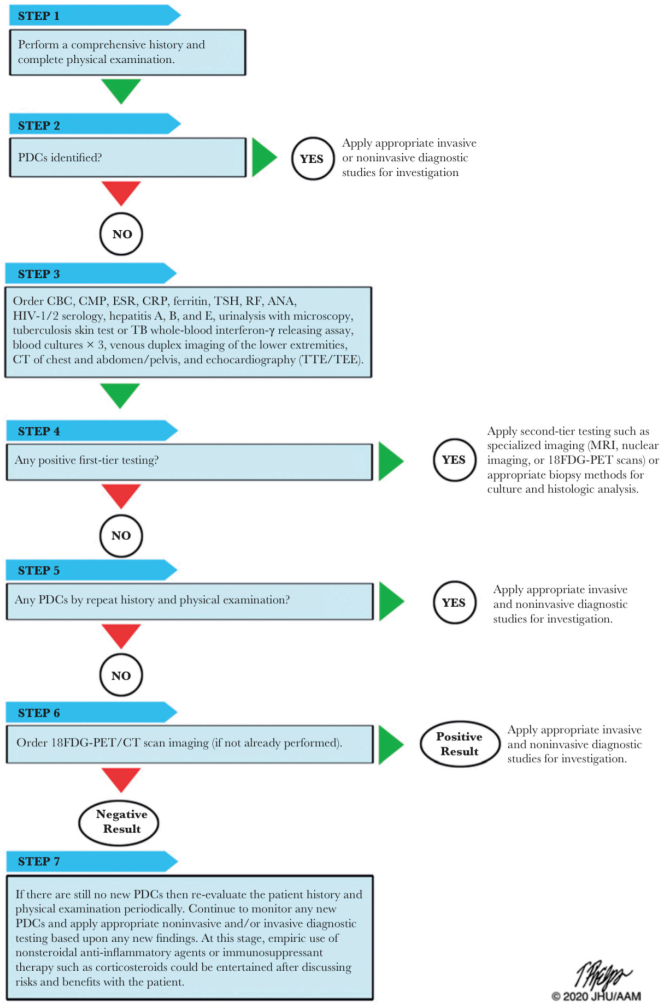

Figure 2. Suggested structured approach to investigating fever of unknown origin cases. This FUO algorithm is based upon limited data [26, 44, 45] and the authors' clinical opinion. Abbreviations: ^{18}FDG-PET, ^{18}fluorodeoxyglucose–positron emission tomography; ANA, antinuclear antibodies; CBC, complete 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 y 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 a favourable outcome, with most patients experiencing resolution of fever within 4 weeks without sequlae.
  - 5-year mortality rates of 3%

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