Fever of Unknown Origin (FUO)

Prof. Russell E. Lewis
Department of Molecular Medicine
University of Padua

russelledward.lewis@unipd.it
https://github.com/Russlewisbo

slides available at: www.padovaid.com

Objectives

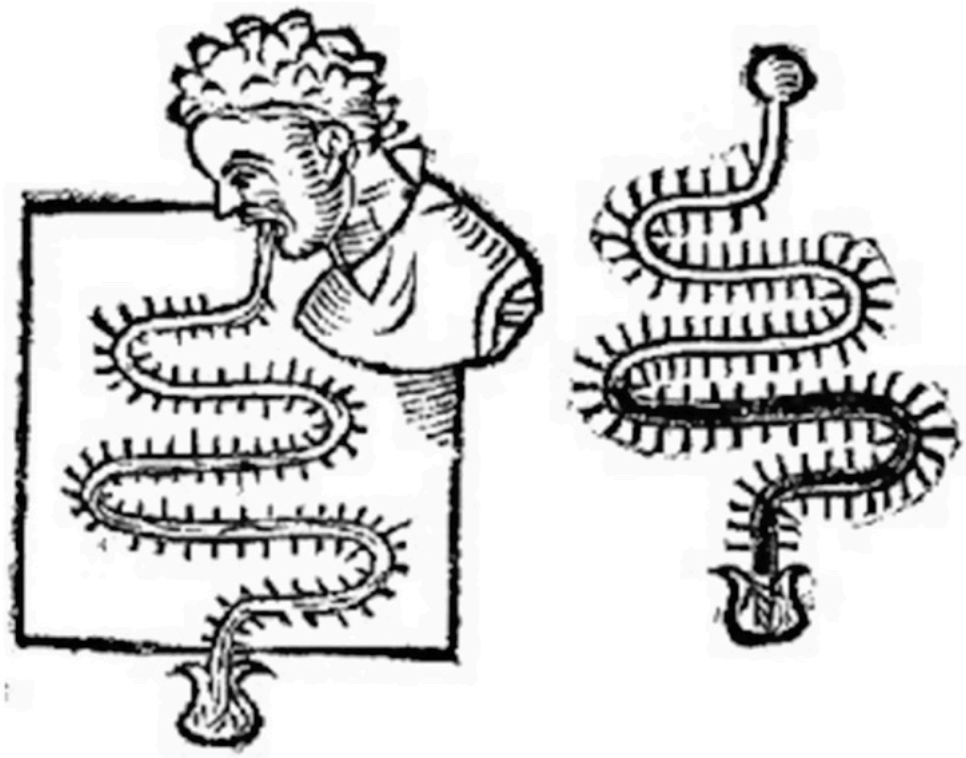
- Recognize leading infectious causes of FUO in key patient groups
- Identify key fever patterns and clinical histories that may direct diagnosis
- Differentiate FUO risks and possible spectrum of pathogens in immunocompromised hosts

The history of fever

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

Early thermometers



A typical design of a thermoscope is a tube in which a liquid rises and falls as the temperature changes.
The Sanctorius thermoscope. Professor Francis Ring, the University of Leeds

Fever in modern medicine

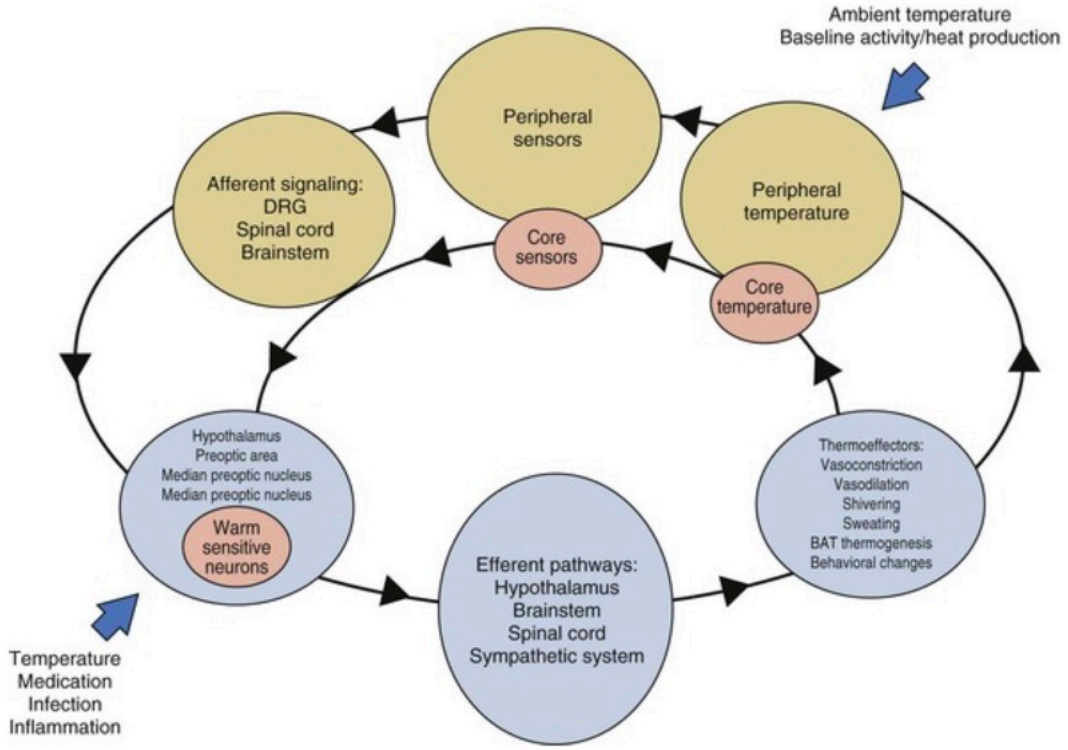
- Wunderlich's pioneering studies of thermometry reported normal temperature at 37°C
- Since the 19th century, humans have become gradually colder - 0.05° to 0.5°C per decade!
  - Current normal range is 36.3 to 36.5°C
- Mackowiak (1992): mean oral temperature 36.8 ± 0.4°C; only 8% had 37°C
- Fever now defined as: early-morning temperature ≥37.2°C or anytime ≥ 37.8°C

Physiologic variables affecting body temperature

- **Age and sex differences**
  - Women ~0.5°C higher at ovulation
  - Infants have higher baseline temperatures
- **Circadian rhythm**
  - Zenith: late afternoon (peak)
  - Nadir: early morning (trough)
- **Other factors**
  - Exercise and physical exertion
  - Medications (antipyretics, corticosteroids)
  - Digestion and recent meals
  - Chronic disease and metabolic conditions

Understanding normal temperature variation is crucial when evaluating a patient for FUO. A temperature of 37.5°C in a patient's early morning

Thermal homeostasis



The hypothalamus acts as the body's thermostat, continuously comparing core temperature against a defended setpoint (~37°C). Afferent thermal signals arrive from both peripheral cutaneous receptors and central thermosensors in the preoptic area of the anterior hypothalamus. When core temperature fa of bodylls below the setpoint, efferent pathways activate heat-conserving and heat-generating responses: cutaneous vasoconstriction reduces radiative heat loss, and shivering thermogenesis in skeletal muscle increases metabolic heat production. When temperature exceeds the setpoint, the balance shifts to heat dissipation: cutaneous vasodilation increases convective and radiative losses, and eccrine sweating provides evaporative cooling. Understanding this

Diurinal pattern of body temperature

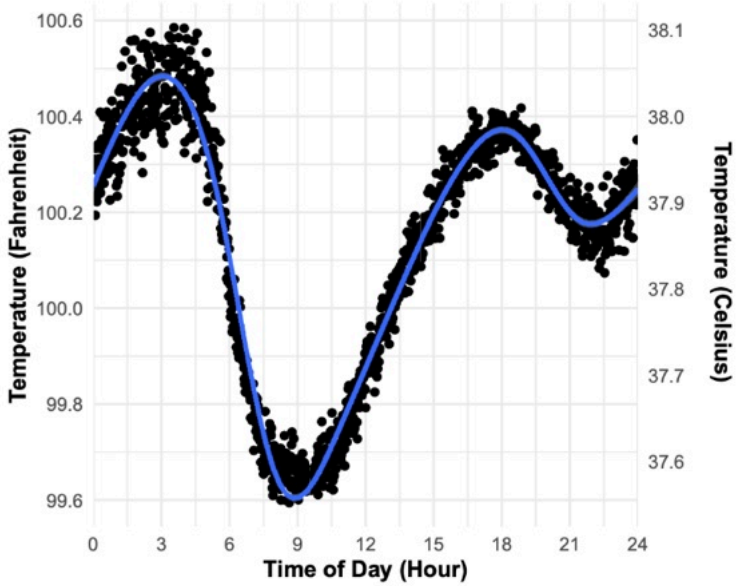
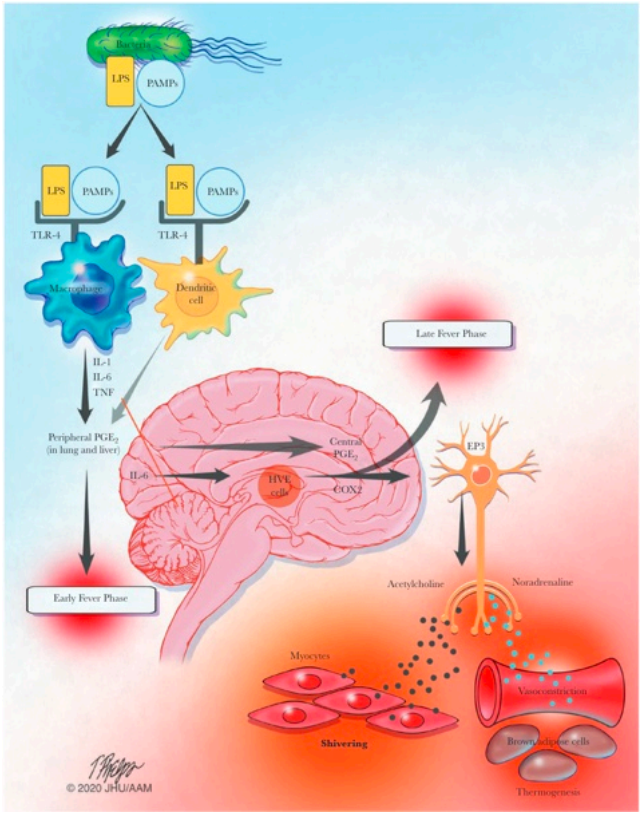


Figure 1: Mean temperature by minute of the day aggregated across all readings and illness episodes. The blue line indicates the smoothed trend from the LOESS model.

Fever vs. Hyperthermia

Feature	Fever	Hyperthermia
Set point	Elevated	Normal
Mechanism	Regulated response	Unregulated heat generation
Cause	Pyrogens (LPS, IL-1, TNF)	Heat exposure, drugs, malignant hyperthermia
Pathophysiology	Altered hypothalamic setpoint	Failure of heat dissipation
Sweating	Absent initially (shivering); later excessive	May be absent
Treatment response	Antipyretics effective	Antipyretics ineffective; cooling required
Examples	Infection, NIID, malignancy	Heat stroke, neuroleptic malignant syndrome

Infection-associated fever - The febrile response



Sequelae of fever - Benefits of fever

- **Phylogenetic conservation** suggests fever is beneficial - appears in ectotherms and endotherms
- **Microbial metabolism** - most pathogenic bacteria are mesophiles (optimal growth at 35-37°C)
  - Even modest temperature elevations slow replication
- **Iron sequestration** - fever triggers hepatic synthesis of hepcidin and lactoferrin
  - Sequesters free iron necessary for bacterial replication
- **Enhanced immune function**
  - Increased neutrophil migration
  - Augmented antibody production
  - Enhanced T-cell proliferation

Rather than viewing fever as purely pathologic, modern immunology reveals it as an important component of the inflammatory response to infection. This

Acute phase proteins

Category	Proteins
↑ **Complement system**	C3, C4, C9, Factor B, C1 inhibitor, C4b-binding protein, Mannose-binding lectin
↑ **Coagulation / fibrinolysis**	Fibrinogen, Plasminogen, tPA, Urokinase, Protein S, Vitronectin, PAI-1
↑ **Antiproteases**	α_1-Protease inhibitor, α_1-Antichymotrypsin, Pancreatic trypsin inhibitor, Inter-α-trypsin inhibitors
↑ **Transport proteins**	Ceruloplasmin, Haptoglobin, Hemopexin
↑ **Inflammatory mediators**	Secreted PLA_2, LPS-binding protein, IL-1 receptor antagonist, G-CSF
↑ **Others**	CRP, Serum amyloid A, α_1-Acid glycoprotein, Fibronectin, Ferritin, Angiotensinogen
↓ **Negative acute-phase**	Albumin, Transferrin, Transthyretin, α_2-HS glycoprotein, Alpha-fetoprotein, Thyroxine-binding globulin, IGF-I, Factor XII

Acute phase phenomena

Category	Phenomena
Neuroendocrine	Fever, somnolence, anorexia; ↑ CRH, corticotropin & cortisol; ↑ arginine vasopressin; ↓ IGF-I; ↑ adrenal catecholamines
Hematopoietic	Anemia of chronic disease; leukocytosis; thrombocytosis
Metabolic	Muscle loss & negative nitrogen balance; ↓ gluconeogenesis; osteoporosis; ↑ hepatic lipogenesis; ↑ adipose lipolysis; ↓ lipoprotein lipase activity; cachexia
Hepatic	↑ Metallothionein, iNOS, heme oxygenase, MnSOD, TIMP-1; ↓ phosphoenolpyruvate carboxykinase activity
Nonprotein plasma	Hypozincemia, hypoferremia, hypercupremia; ↑ plasma retinol & glutathione

Epidemiology of FUO - Definitions

Category	Key causes / definition
Classic FUO	Infection (TB, endocarditis, occult abscess, zoonoses, enteric fever, syphilis, histoplasmosis), malignancy, autoimmune/autoinflammatory, miscellaneous; includes virally suppressed HIV (CD4 >200)
Nosocomial FUO	FUO arising in hospitalized patients
ICU	Bacteremia, pneumonia, *C. difficile*, fungemia, catheter infections, PE, acalculous cholecystitis, drug fever, stroke/intracranial hemorrhage
Non-ICU	Similar to ICU causes; patient not critically ill
Immunodeficiency-associated FUO	Highly variable; depends on type and degree of immunodeficiency
Organ-transplant recipients	Viruses, donor-derived infections, *Strongyloides* hyperinfection, opportunistic fungi, rejection, GVHD, HLH, ureaplasma hyperammonemia
Neutropenia	Febrile >5 days despite empirical antibiotics; influenced by neutropenia duration, GVHD prophylaxis, antimicrobial agents
HCT recipients	Pre-engraftment: neutropenic causes; early post-engraftment: herpesvirus, adenovirus, hyperacute GVHD, pneumonia; late: relapsed cancer, immune reconstitution
HIV/AIDS (no ART)	Acute retroviral syndrome, mycobacteria, endemic mycoses, toxoplasmosis, cryptococcosis, HHV-8–associated diseases, lymphoma
Travel-associated FUO	Malaria, enteric fever, leptospirosis, viral hemorrhagic fevers, typhus, undifferentiated tropical febrile illness

(Haidar and Singh, 2022)

Fever therapy to treat syphilis

- Treponema pallidum is uniquely sensitive to increased temperatures
- Using effective anti-malarial drugs to control the P. vivax infection, while maintaining the fever it causes to the detriment of other, ongoing, and then-incurable infections present in the patient, such as late-stage syphilis
- Treponema pallidum is uniquely sensitive to increased temperatures
- Using effective anti-malarial drugs to control the P. vivax infection, while maintaining the fever it causes to the detriment of other, ongoing, and then-incurable infections present in the patient, such as late-stage syphilis
- This type of pyrotherapy was most famously used by psychiatrist Julius Wagner-Jauregg, who won the Nobel Prize for Medicine in 1927 for his elaboration of the procedure in treating neurosyphilis

Classic FUO

- **Definition:**
  - Temperature of > 38.3℃ > 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

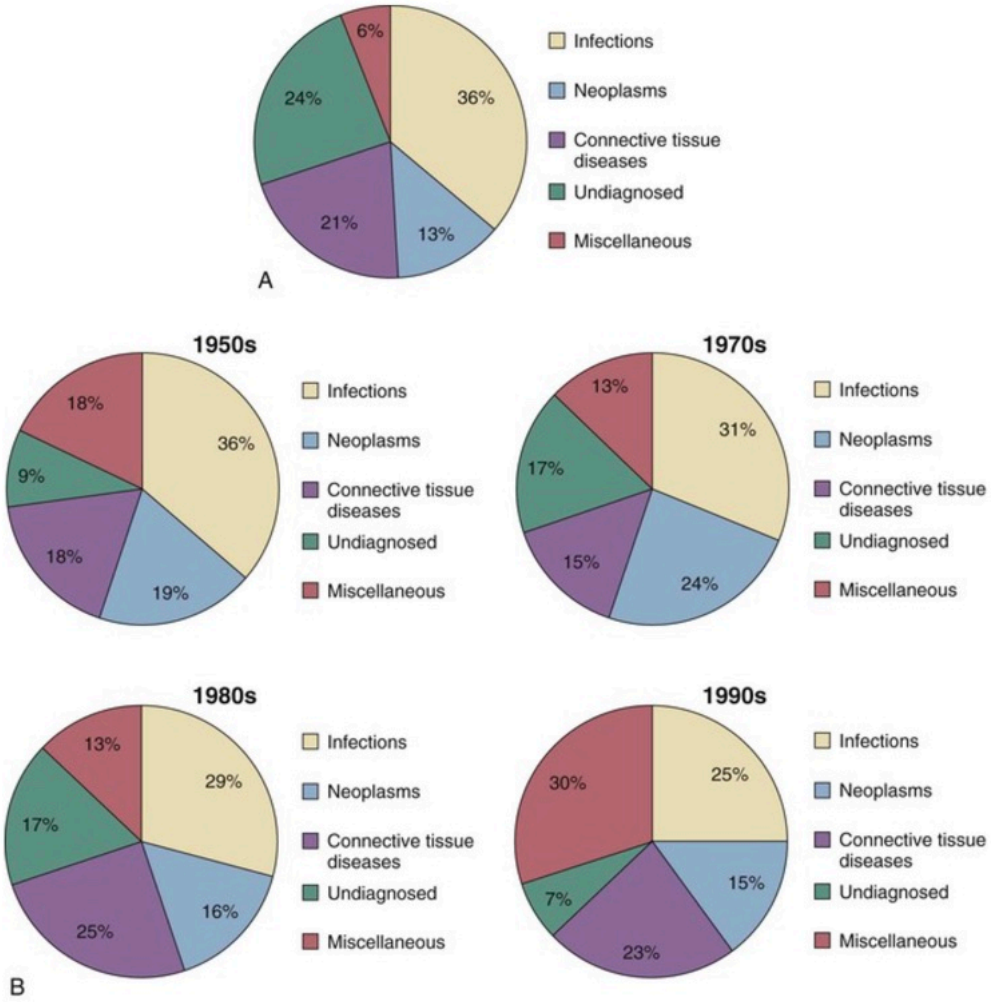


FIGURE 56-1 **A,** Frequency of the five main etiologic categories of fever of unknown origin. **B,** Frequency of the five main etiologic categories of fever of unknown origin by decade. (**A** from Hayakawa K, et al. Fever of unknown origin: an evidence-based review. *Am J Med Sci.* 2012;344:307-316; **B** from Mourad O, Palda V,

Classic FUO - Infectious Etiology

- **Chronic or relapsing infections**
  - Occult abscess (intra-abdominal, hepatic, splenic, renal, perirectal)
  - Endocarditis (both native and prosthetic valve)
  - Tuberculosis (pulmonary and extrapulmonary)
  - Complicated urinary tract infections (pyelonephritis, prostatitis)
  - Osteomyelitis (especially vertebral)
  - Other: brucellosis, leptospirosis, syphilis, bartonellosis

Rare and miscellaneous causes of fever

Category	Examples
Autoinflammatory / periodic fevers	Adult-onset Still's disease, Behçet's syndrome, Familial Mediterranean fever, Familial Hibernian fever, Periodic fever, Schnitzler's syndrome
Vascular / cardiac	Aortic dissection, Aortitis, Atrial myxoma, Giant coronary aneurysm, Pericarditis, Postpericardiotomy syndrome, Polyarteritis nodosa, Pulmonary emboli, Veno-occlusive disease
Hematologic / oncologic	Castleman's disease, Cyclic neutropenia, Hemoglobinopathies, Hemolytic anemias, Hemophagocytic syndrome, Histiocytosis X, Immunoblastic lymphadenopathy, Lymphomatoid granulomatosis, Myeloproliferative syndromes, Paroxysmal hemoglobinurias, Rosai-Dorfman disease, TTP
Granulomatous / lymphoproliferative	Allergic alveolitis, Granulomatous hepatitis, Granulomatous peritonitis, Kikuchi-Fujimoto disease, Lofgren syndrome, Retroperitoneal fibrosis, Sarcoidosis, Subacute necrotizing lymphadenitis
Autoimmune / rheumatologic	Autoimmune cholangitis, Erythema multiforme, Inflammatory bowel disease, Serum sickness, Sjögren's syndrome, Wegener's granulomatosis
Endocrine / metabolic	Addison's disease, Fabry's disease, Parathyroid apoplexy, Pheochromocytoma, Thyroiditis & thyrotoxicosis, Vitamin B_{12} deficiency
GI / hepatic	Alcoholic hepatitis, Cirrhotic fever, Pancreatitis
Infectious	Bartonellosis, Carcinomatous meningitis, Chronic meningitis, Hantavirus, Human picornavirus, Hypereosinophilic syndrome, Infected urachal cyst, Sinusitis, Whipple's disease

Uncommon and rare causes of FUO

Category	Examples
Infections	Bartonellosis, hantavirus, coccidioidomycosis, histoplasmosis, blastomycosis, cysticercosis
NIID	Addison disease, Behçet syndrome, SLE, vasculitis, inflammatory bowel disease, GPA, sarcoidosis, Sjögren syndrome, thyroiditis, adult-onset Still disease
Malignancy	Atrial myxoma, lymphoma, leukemia, pheochromocytoma, Schnitzler syndrome
Other	Cirrhotic fever, drug fever, factitious fever, vitamin B_{12} deficiency, pulmonary embolism

Classic FUO in infants and children

- **Respiratory tract infections** - viral, atypical organisms
- **Other infections:**
  - UTIs (especially important in young girls)
  - Brucellosis, tuberculosis, bartonellosis
- **Systemic inflammatory conditions:**
  - Kawasaki disease (critical, age < 5 years)
  - Inflammatory bowel diseases
  - Still's disease (juvenile rheumatoid arthritis)
- **Note:** Connective tissue diseases and cancers are generally rare in children
- **Important:** Joint involvement is a sign of serious disorder - consider endocarditis, leukemia, connective tissue disease

Classic FUO in elderly patients

- **In developed countries: connective tissue diseases > infections**
  - Temporal arteritis (critical diagnosis - risk of blindness)
  - Polymyalgia rheumatica
  - Other vasculitides
- **Diagnostic challenge:** symptoms are subacute and non-specific, easily attributed to aging
- **Infections still important:**
  - Intra-abdominal abscess
  - Complicated UTIs (often without pyuria)
  - Tuberculosis (may be reactivation)
  - Endocarditis (prosthetic valves more common in elderly)
- **Malignancy:** solid tumors and hematologic malignancies increase with age

Returning travelers

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

In the returning traveller with FUO, the incubation period and geographic exposures are paramount. Malaria, dengue, typhoid, leptospirosis, and rickettsial infections should be high on the differential based on travel

Nosocomial (Health-Care Associated) FUO

- **Leading causes:**
  - Drug fever (especially to antibiotics, anti-epileptic medications)
  - Post-operative complications (e.g., occult abscess, anastomotic leak)
  - Decubitus ulcers with superimposed infection
  - Septic thrombophlebitis (peripherally inserted central catheters)
  - Recurrent pulmonary emboli
  - Myocardial infarction
  - Hematologic malignancy (newly diagnosed during hospitalization)
  - Blood transfusion reaction
  - Reactions to contrast media used in radiologic procedures
  - *Clostridium difficile* colitis

Fever in post-operative patients

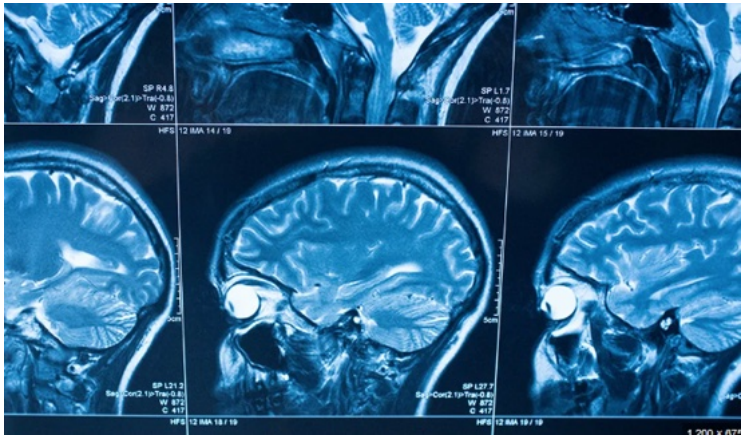
- **Epidemiology:** > 1/3 of patients manifest fever in first 5 days post-surgery
- **Infectious vs. non-infectious:** < 10% of febrile patients have an identified source or positive cultures
- **Pathophysiology:** Fever may represent a physiological response to surgically-induced tissue injury
  - Release of pyrogenic cytokines and interleukins
  - Not necessarily indicative of infection
- **Clinical pearl:** Early fever (post-op day 1-3) is usually non-infectious; later fever (day 5+) warrants infection investigation

FUO in ICU patients

- **Early fevers are common** and often non-infectious
  - Associated with good prognosis
  - Related to inflammatory response to critical illness
- **Prolonged fever carries a poorer prognosis**
- **Common complications:**
  - Sinusitis (from mechanical ventilation, supine positioning, feeding tubes)
  - Ventilator-associated pneumonia
  - Catheter-related bloodstream infections
- **Other causes similar to nosocomial FUO**
  - Abscess, drug fever, septic thrombophlebitis, pulmonary emboli

FUO in stroke patients

- **Non-infective fevers are common** in stroke patients
  - Occur earlier after stroke than infection
  - Related to hypothalamic injury and cytokine release
- **Infection-related complications:**
  - UTI (from urinary catheterization)
  - Aspiration pneumonia
  - DVT/PE
- **Clinical challenge:** Distinguishing fever from infarct-related inflammation vs. infection can be difficult; broad-spectrum antibiotics often given empirically



FUO in neutropenic patients

- **ANC = Total WBC x (% Segs + % Bands)**
- **Definition of neutropenia:**
  - ANC < 500 cells/mm^3
  - "Profound" neutropenia: ANC < 100 cells/mm^3
- **Frequency of fever during chemotherapy-induced neutropenia:**
  - 10-50% of patients with solid tumors
  - 80% of those with hematologic malignancies during ≥1 chemotherapy cycle
  - Most patients will have NO infectious etiology documented
- **Critical finding:** Signs of inflammation are notoriously absent other than fever
  - No exudate, no fluctuance, no purulent drainage
  - Makes clinical diagnosis extremely difficult

This is one of the most challenging patient populations. The absence of typical signs of infection makes physical examination nearly useless, and a single positive blood culture in a neutropenic patient must be treated as bacteremia until proven otherwise. Prompt empiric broad-spectrum antibiotics (before

Clinical manifestations of infection related to absolute neutrophil count

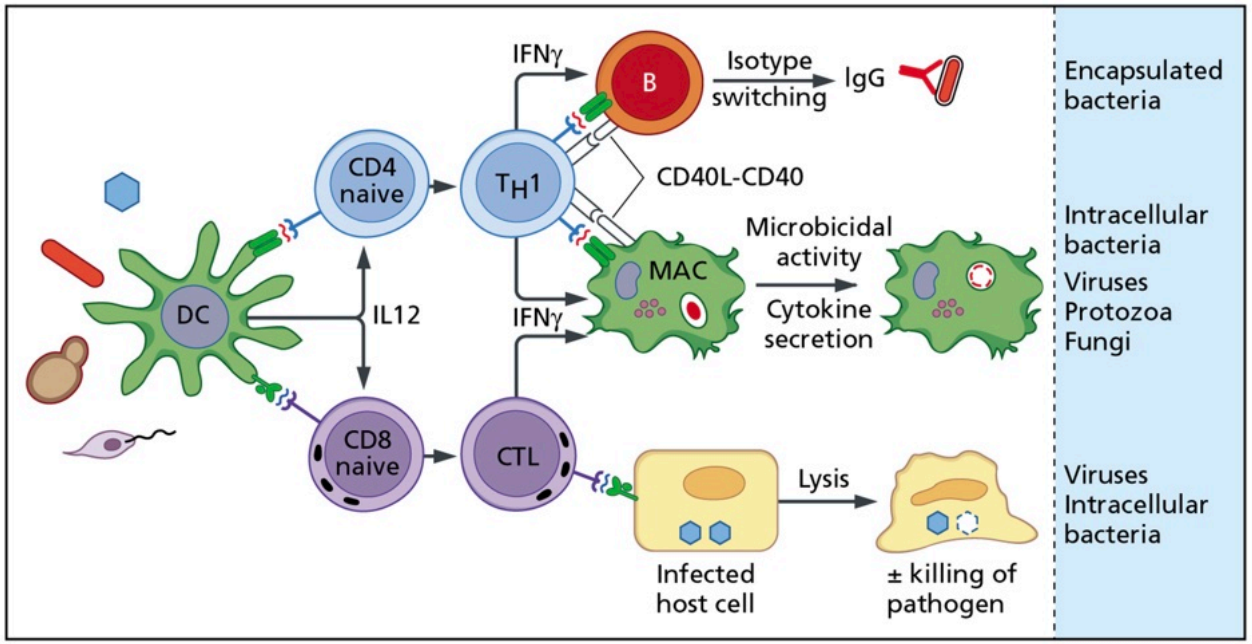
Sign/Symptom	Type of Infection	% with ANC<100	% with ANC>1000
Fever	Overall	98	76
Bacteremia	Overall	43	13
Fluctuance	Anorectal	8	67
Exudate	Skin	5	92
Purulent sputum	Pneumonia	8	84
Pyuria	UTI	11	97

(Sickles et al., 1975)

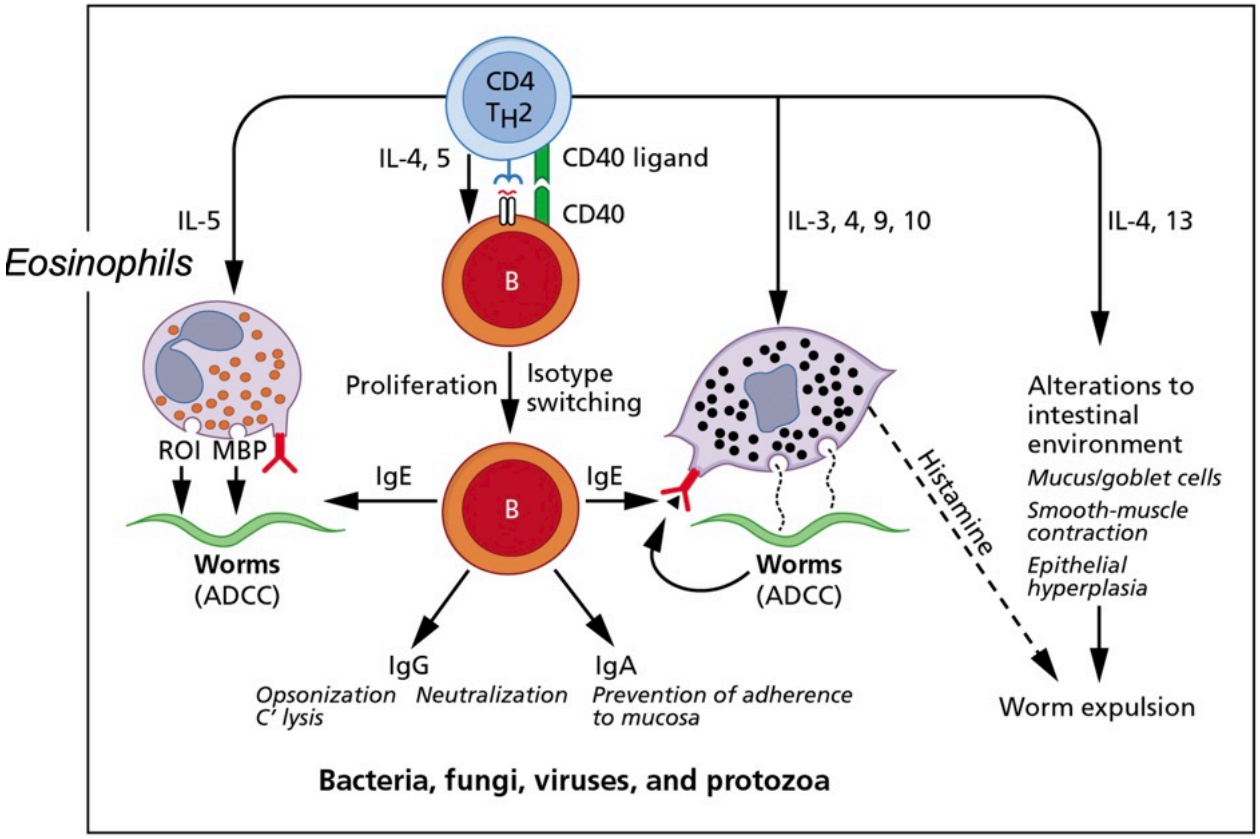
Possible causes of fever in neutropenic patients not responding to broad-spectrum antibiotics

Cause	Approx. frequency in high-risk patients
Fungal infections susceptible to empirical therapy	40%
Bacterial infections (cryptic foci, biofilms, resistant organisms)	10%
GVHD after hematopoietic stem cell transplantation	10%
Fungal infections resistant to empirical antifungal therapy	5%
Toxoplasma gondii, mycobacteria, or fastidious pathogens (*Legionella*, *Mycoplasma*, *Chlamydia pneumoniae*, *Bartonella*)	5%
Viral infections (herpesviruses, CMV, EBV, HHV-6, VZV, HSV, parainfluenza, RSV, influenza)	5%
Undefined (drug fever, chemotherapy toxicity, antitumor responses, undefined pathogens)	**25%**

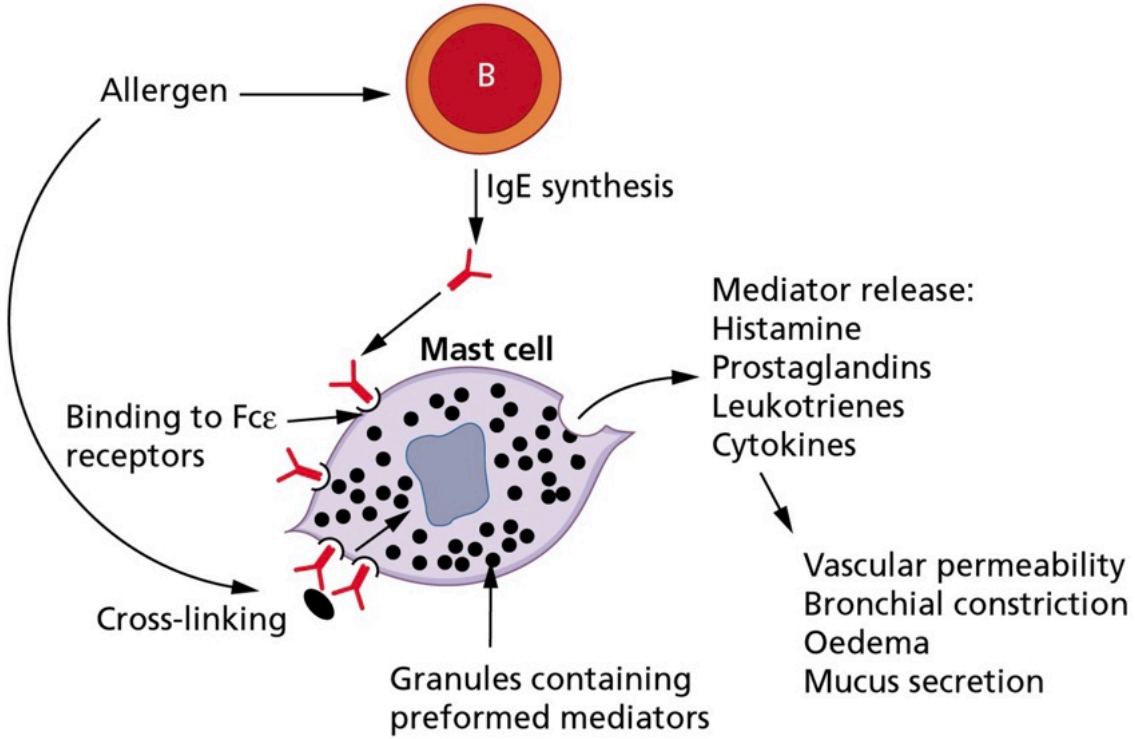
Cell-mediated immunity - Th1 pathway



Cell-mediated immunity - Th2 pathway



Cell-mediated immunity - Drug allergy (Type IV hypersensitivity)



Infections in immunocompromised hosts

Infections in Immunocompromised Hosts

Authors: Kathryn Bedard, MD*@KatieBedardMD, Charmaine Mutucumarana, MD* Eva Amenta, MD* @EvaAmenta, Nico Cortes-Penfield, MD @Cortes_Penfield, Deeksha Jandhyala, MD @transplantID, Prathit Kulkarni, MD @PrathitKulkarni
(*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

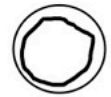
Steroids (dose- and duration-dependent)
Generalized increased risk of infection
(Ppx Bactrim if ≥20 mg/day for ≥3 weeks)
- Candida, VZV, TB, PJP, molds, Strongyloides

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

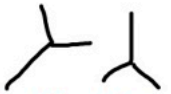
<150
- Histoplasmosis

<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 infection phase** characterized by mononucleosis-like illness
  - Fever is common
  - May be undiagnosed if it precedes seroconversion (acute retroviral syndrome)
- **Later phases of untreated HIV**
  - Episodes of fever become common
  - Often signify superimposed illness - e.g., opportunistic infections
  - Infections may manifest atypically
- **HAART era impact**
  - Once highly-active antiretroviral therapy (HAART) is started
  - Effective suppression of HIV viral load
  - Frequency of FUO falls markedly
  - CD4 recovery allows control of opportunistic infections

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

Etiology	No. (%)
Infection	**63 (88%)**
DMAC	22 (31%)
Pneumocystis jirovecii pneumonia	10 (13%)
CMV	8 (11%)
Histoplasmosis	5 (7%)
Viral (not CMV)	5 (7%)
Bacterial	4 (5%)
Mycobacterium tuberculosis	4 (5%)
Fungal (not histoplasmosis)	2 (3%)
Parasitic	2 (3%)
Mycobacterium genavense	1 (1%)
Neoplasia	**6 (8%)**
Lymphoma	5 (7%)
Kaposi sarcoma	1 (1%)
Miscellaneous	**3 (4%)**
Drug fever	2 (3%)
Castleman disease	1 (1%)

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

- **Indications for trial:**
  - Temperature > 37.8°C at least once daily for ≥2 weeks
  - Lack of evidence of infection (physical exam, labs, imaging)
  - Absence of drug fever, transfusion reaction, or allergic mechanisms
  - Lack of response to ≥7 days of empiric antibiotics
- **Procedure:**
  - Naproxen 500 mg BID × 3-5 days
- **Positive result:**
  - Prompt complete defervescence (lysis of fever)
  - Sustained normal temperature while receiving naproxen
  - Fever recurrence when drug discontinued
- **Note:** Not universally accepted; sensitivity/specificity debated

Diagnosis of FUO

General diagnostic evaluation of FUO

Step	Investigation
History & Exam	Comprehensive history; repeated physical exams
Laboratory	CBC, comprehensive metabolic panel, urinalysis with microscopy
Inflammatory Markers	ESR, C-reactive protein
Autoimmune Screening	ANA, rheumatoid factor
Imaging - First Line	Chest radiograph, CT abdomen/pelvis
Cultures	Blood cultures (3 specimens without antimicrobials), urine culture
Serologies	CMV IgM/PCR, heterophil antibody (EBV) in young adults
Tuberculosis	Tuberculin skin test, interferon-gamma release assay
Advanced Imaging	MRI, PET-CT, duplex ultrasound lower extremities
Invasive Procedures	Biopsy (lymph node, liver, bone marrow) if indicated

The history and physical examination must guide which investigations to pursue, otherwise the patient will undergo excessive and often unnecessary testing with false positives leading to misdirected therapy.

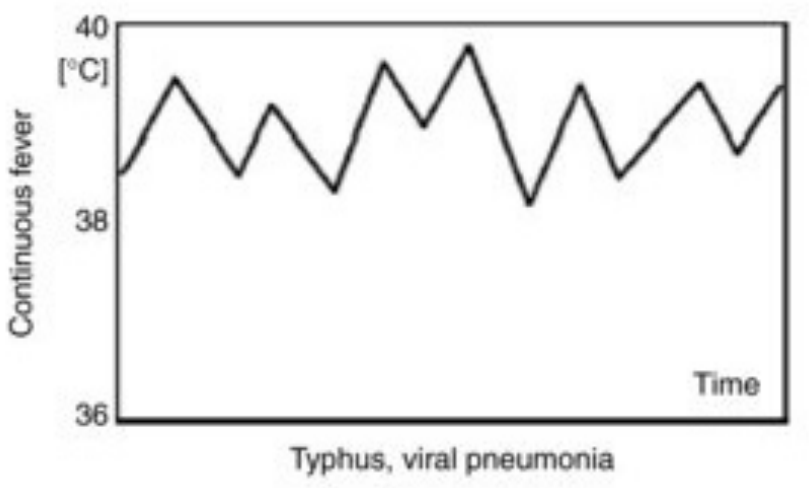
Patient history

- **Helps guide choice of initial laboratory investigations** - this is the most important step
- **Travel history:** where, when, duration, exposures to animals, arthropod vectors, contaminated water
- **Exposure to animals and work environment:** pet birds (psittacosis), cats (toxoplasmosis, bartonellosis), tick exposure (Lyme, Q fever)
- **Recent contact with ill persons** or family history of FUO (e.g., familial Mediterranean fever)
- **Complete medication list:** including OTC drugs, supplements, recent antimicrobials
- **Prior history of FUO** - may be recurrence of same diagnosis
- **Previously diagnosed conditions:** malignancy, rheumatic fever, valve disease that predisposes to endocarditis

Verification of fever and pattern of fever

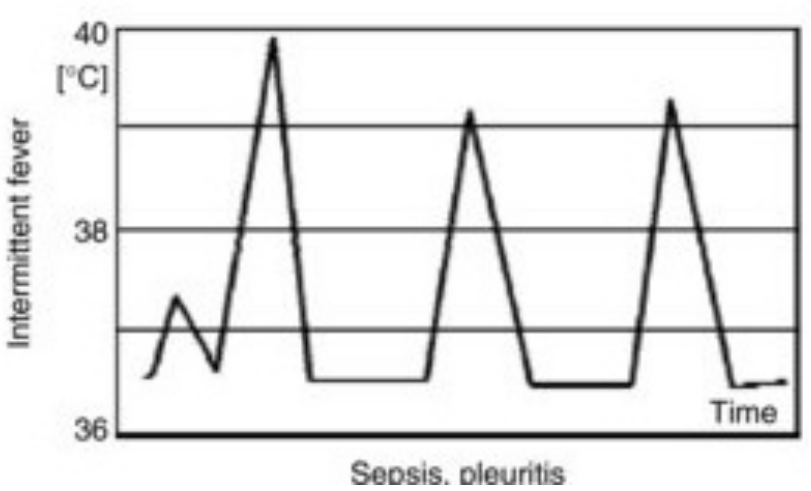
- **Verification of fever:** Often overlooked step
  - In some series, up to 30% referred for FUO where determined to NOT have fever
  - Request fever log or have patient take temperatures at home
- **Fever patterns** - use of patterns to narrow differential:
  - *Continuous, remittent, intermittent, hectic (Charcot's), quotidian, quartan, biphasic (saddleback), Pel-Ebstein*
- **Factors affecting fever pattern:**
  - Hydration status, ambient temperature
  - Accuracy of temperature measurements (different sites)
  - Antipyretics and corticosteroids suppress fever
  - Blood transfusions and other medical interventions

Continuous sustained fever



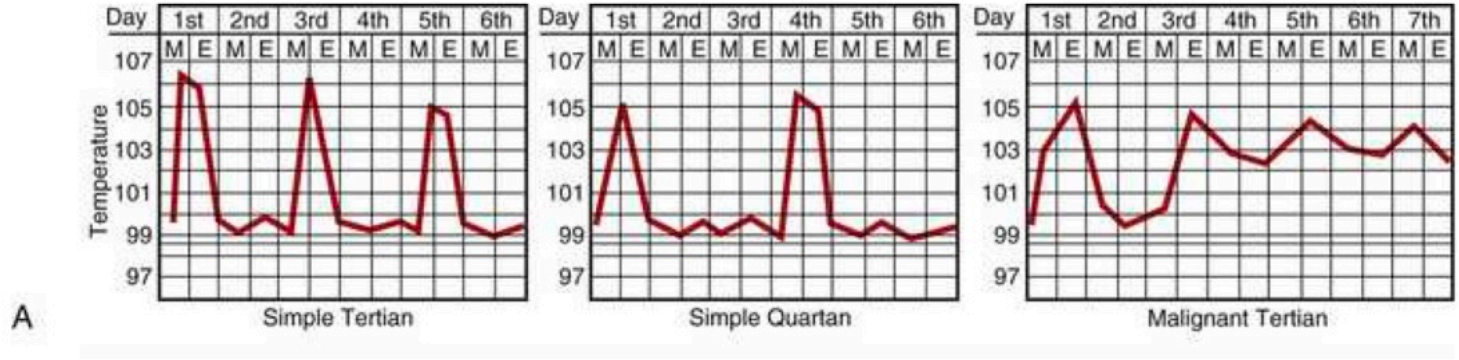
- Continuous fever with slight remission not exceeding 2°C
  - Lobar and gram-negative pneumonia
  - Rickettsiosis
  - Typhoid fever
  - CNS disorders
  - Tularemia
  - Falciparum (malignant tertian) malaria

Intermittent (quotidian) fever



- Intermittent 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 may present with daily (quotidian), every 3rd day (tertian), or every 4th day (quartan) patterns
  - Double quotidian pattern (two daily spikes) seen with:
    - Salmonellosis
    - Miliary tuberculosis
    - Double malarial infections (>1 species)
    - Gonococcal and meningococcal endocarditis

Malaria fever - Paroxysmal patterns



Febrile paroxysms may occur every other day for *P. vivax*, *P. ovale*, and *P. falciparum* (tertian fever) and every third day for *P. malariae* (quartan fever).

Paroxysms occurring at regular intervals are more common in *P. vivax* or *P. ovale* than *P. falciparum*. With improvements in early diagnosis and treatment, this traditional description of cyclic fever is seen infrequently.

The regular paroxysmal pattern of malaria fever historically served as a diagnostic clue, but modern rapid diagnostic tests have made fever pattern analysis

Saddle-back (biphasic) fever

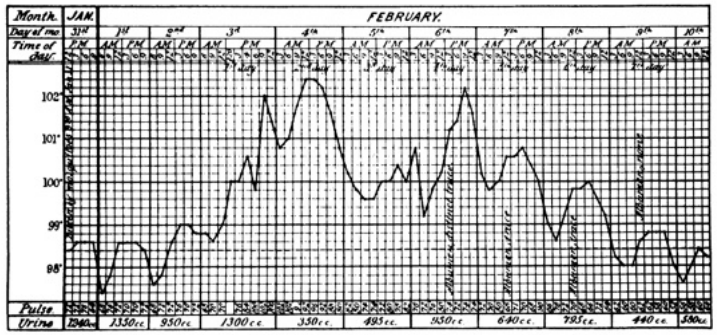
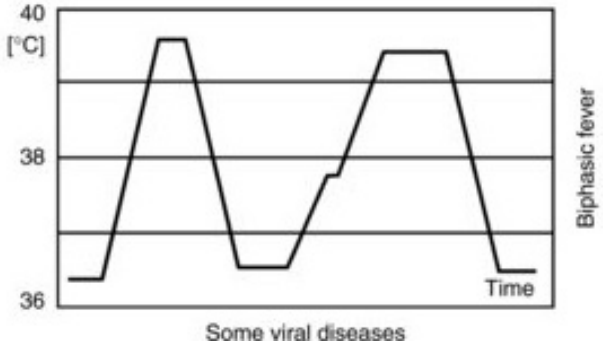


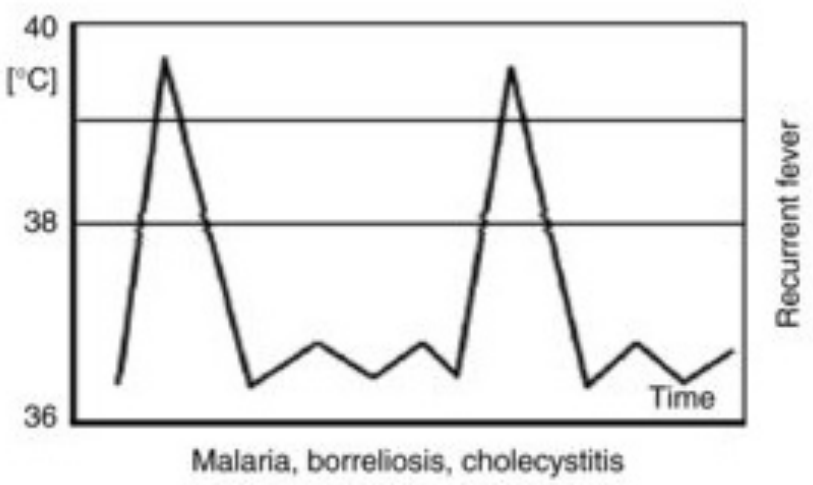
Figure 4. Plot of a saddle-back (biphasic) fever in a patient with yellow fever. (Reprinted from Reed W., et al. Experimental yellow fever. Am Med 1901;III:12.)



Some viral diseases

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

Intermittent hectic (Charcot's) fever



- Sporadic episodes of fever with periods of normal temperature and recurrence
  - Frequently seen in cholangitis associated with cholelithiasis
  - Classic teaching: jaundice, fever, right upper quadrant pain (Charcot's triad)
  - Often associated with leukocytosis and toxic appearance

Undulating (Pel-Ebstein) fever

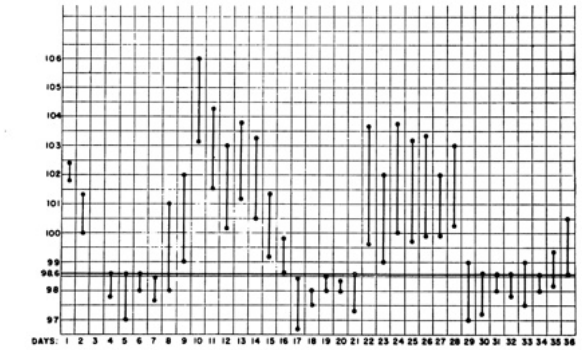
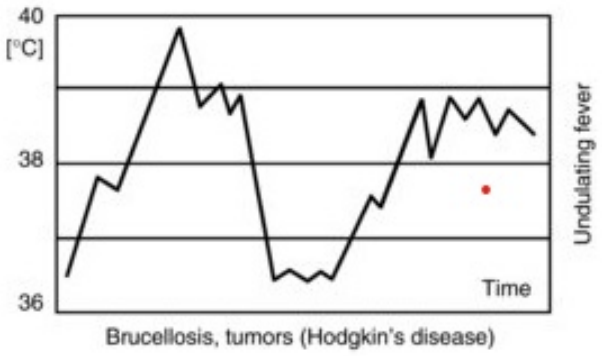
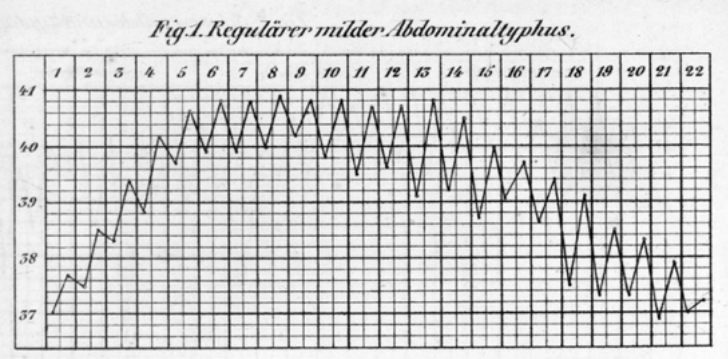


Figure 5. Plot of a Pel-Ebstein fever in a patient with Hodgkin's disease. (Reprinted with permission from Kampmeier RH, Blake TH. Physical examination in health and disease. 4th ed. Philadelphia: FA Davis, 1970:124–5.)



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

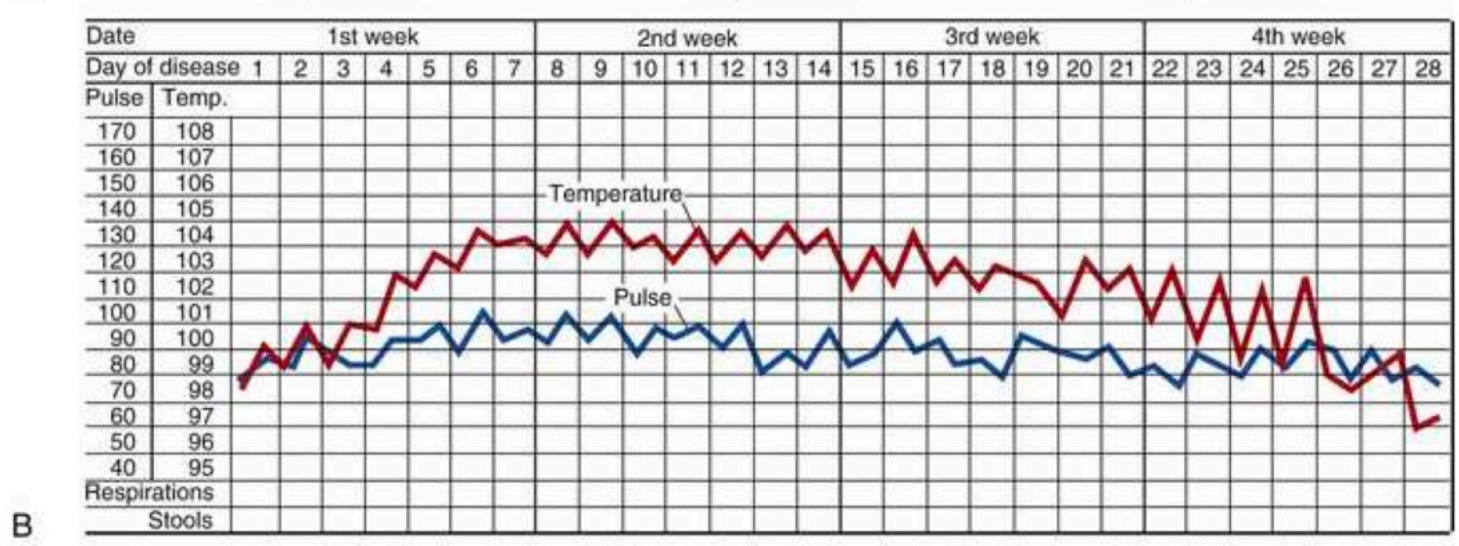
Typus Inversus



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

Typus inversus is an unusual pattern but when present strongly suggests one of the listed diagnoses. Its presence should prompt investigation for

Typhoid fever - Step-ladder fever

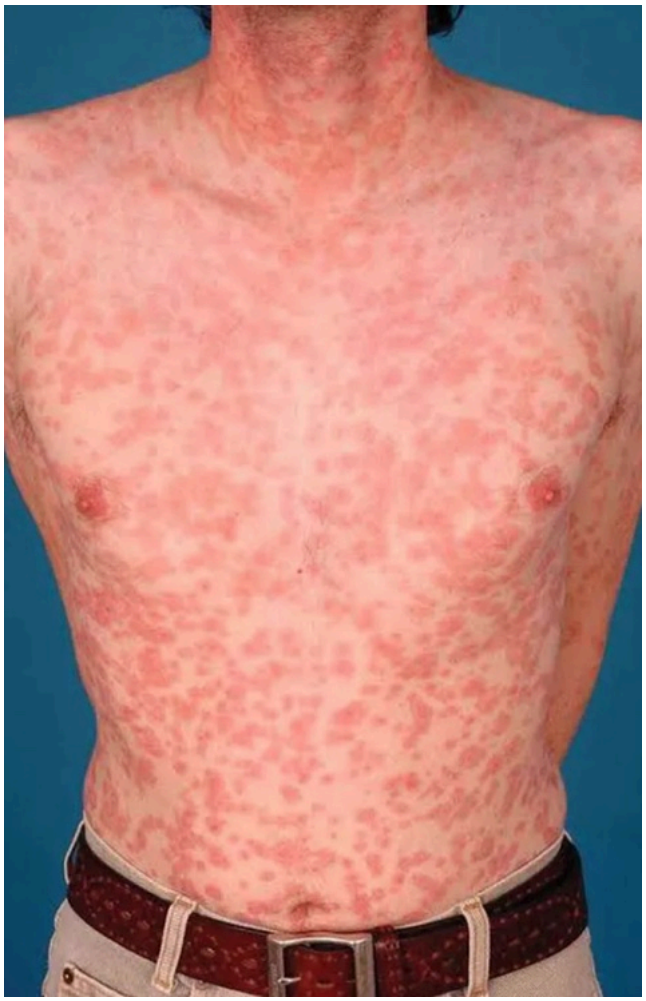


B

The classic teaching of typhoid's step-ladder fever (progressively higher fever each day for 3-4 days until reaching a plateau) is less commonly observed in modern cases, possibly due to partial treatment with antipyretics or other antimicrobials before diagnosis. However, when present, it is highly suggestive

Jarisch-Herxheimer reaction

- **Definition:** Sharply increased elevation of temperature with rigors, chills, and constitutional symptoms occurring within hours of starting antibiotic therapy
- **Mechanism:** Lysis of spirochetes (or other organisms) releases endotoxin triggering acute inflammatory response
- **Organisms associated:**
  - Primary or secondary syphilis
  - Leptospirosis
  - Tick-borne relapsing fever (*Borrelia*)
  - Tetracycline or chloramphenicol therapy for acute brucellosis
- **Clinical significance:** Can be severe enough to cause hemodynamic compromise; does not indicate treatment failure



Physical examination

- Some signs are subtle and may require repeated exams to be appreciated
- Vigorous search for lymphadenopathy (consideration for biopsy)
- Careful examination of fundi, oropharynx, temporal arteries, abdomen, spleen, joints, skin, nails, genitalia

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 / conjunctivae	Choroid tubercle, petechiae, Roth's spot	Disseminated granulomatosis, endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
Abdomen	Enlarged iliac lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis
Rectum	Perirectal / prostatic fluctuance, tenderness	Abscess
Genitalia	Testicular nodule; epididymal nodule	Periarteritis nodosa; disseminated granulomatosis
Lower extremities	Deep venous tenderness	Thrombosis / thrombophlebitis
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

Laboratory investigations

"The cause of FUO is more frequently a *common disease* presenting in an *atypical fashion* than a *rare disease* presenting *in a typical fashion*."

- Multiple diagnostic algorithms exist in literature
- Must be selectively applied or will result in excessive unfocused diagnostic testing
  - False positives lead to misdiagnosis
  - Misguided treatment plans
- **"Sutton's Law"** - pursue most likely diagnosis first based on history and epidemiology
- History and physical exam (most important) should guide choice and sequence of tests

Shotgun laboratory approach to FUO is expensive, time-consuming, and counterproductive. A focused history-driven approach is far more efficient. This

Examples of potential diagnostic clues (1/3)

Etiology	Historical clues	Physical clues
Anaplasmosis	*Ixodes* tick bite; outdoor activity in North Central / Eastern US	Fever, headache, arthralgia, myalgia, pneumonitis, thrombocytopenia, lymphopenia, ↑ liver enzymes
Babesiosis	*Ixodes* tick bite; outdoor activity in Northeastern US	Arthralgias, myalgias, relative bradycardia, hepatosplenomegaly, anemia, thrombocytopenia, ↑ liver enzymes
Bartonellosis	Travel to Andes (Oroya fever; *B. bacilliformis*); homelessness (*B. quintana*); scratch from infected kitten/cat (*B. henselae*)	Conjunctivitis, retro-orbital pain, anterior tibial bone pain, macular rash, nodular plaque lesions, regional lymphadenopathy
Blastomycosis	Contact with soil near Mississippi/Ohio River valleys, Saint Lawrence River, or Great Lakes; exposure to infected dogs	Arthritis, atypical pneumonia, pulmonary nodules, ARDS, verrucous/nodular/ulcerative skin lesions, prostatitis
Brucellosis	Contact with/consumption of products from infected goats, pigs, camels, yaks, buffalo, cows; abattoir work	Arthralgias, hepatosplenomegaly, suppurative musculoskeletal lesions, sacroiliitis, spondylitis, uveitis, hepatitis, pancytopenia
Coccidioidomycosis	Exposure to soil or dust in the southwestern US	Arthralgias, pneumonia, pulmonary cavities, pulmonary nodules, erythema multiforme, erythema nodosum
Ehrlichiosis	*Amblyomma*, *Dermacentor*, or *Ixodes* tick bite; outdoor activity in midwestern / southeastern US	Pneumonitis, hepatitis, thrombocytopenia, lymphopenia

Examples of potential diagnostic clues (2/3)

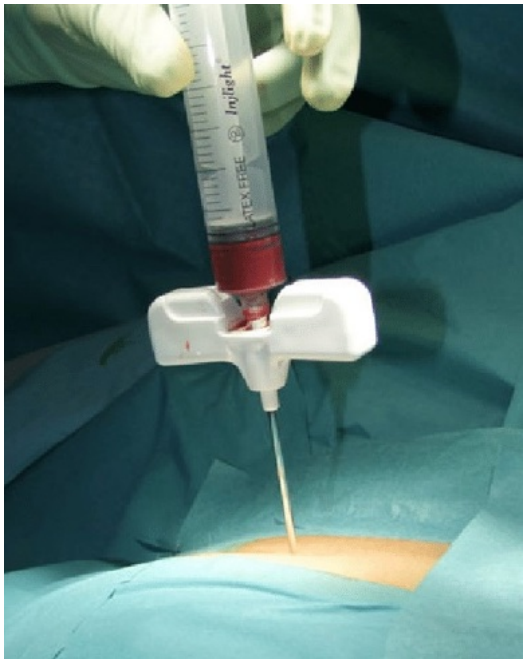
Etiology	Historical clues	Physical clues
Enteric fever (*Salmonella* Typhi)	Recent travel to endemic country; consumption of potentially contaminated food or water	Headache, arthritis, abdominal pain, relative bradycardia, hepatosplenomegaly, leukopenia
Histoplasmosis	Exposure to bat/blackbird excreta in roosts, chicken houses, or caves; Ohio and Mississippi River valleys	Headache, pneumonia, pulmonary cavities, mucosal ulcers, adenopathy, erythema nodosum, erythema multiforme, hepatitis, anemia, leukopenia, thrombocytopenia
Leptospirosis	Occupational exposure in sewers, rice/sugar cane fields, abattoirs; recreational water sports; contact with contaminated water or infected dogs	Bitemporal/frontal headache, calf and lumbar muscle tenderness, conjunctival suffusion, hepatic and renal failure, hemorrhagic pneumonitis
Leishmaniasis (visceral)	Recent travel to sand fly–endemic areas	Hepatosplenomegaly, lymphadenopathy, hyperpigmentation of face/hands/feet/abdomen (kala azar)
Malaria	Recent travel to endemic areas in Asia, Africa, or Central/South America	Fever, headaches, nausea, vomiting, diarrhea, hepatosplenomegaly, anemia
Psittacosis (*Chlamydia psittaci*)	Contact with birds, especially psittacine birds	Fever, pharyngitis, hepatosplenomegaly, pneumonia, blanching maculopapular eruptions, erythema multiforme, erythema marginatum, erythema nodosum

Examples of potential diagnostic clues (3/3)

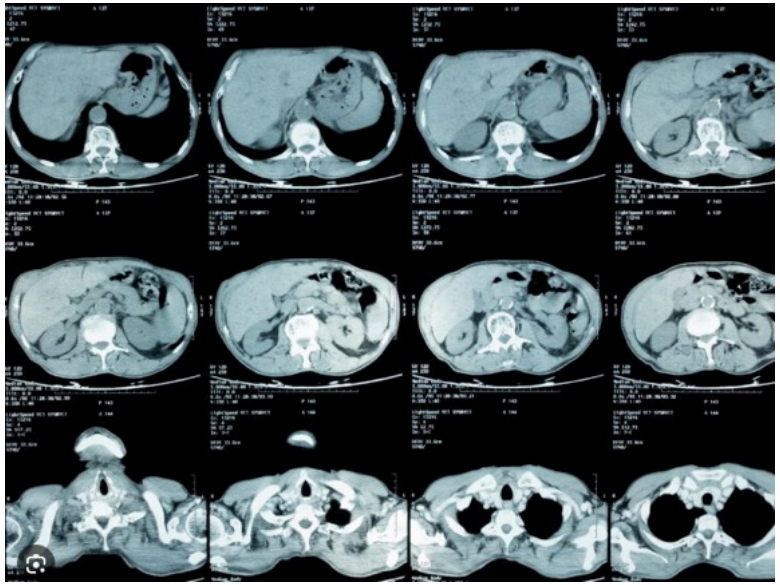
Etiology	Historical clues	Physical clues
Q fever (*Coxiella burnetii*)	Farm, veterinary, or abattoir work; unpasteurized milk; contact with infected sheep, goats, or cattle	Atypical pneumonia, hepatitis, hepatomegaly, relative bradycardia, splenomegaly
Rat-bite fever (*Streptobacillus moniliformis*)	Recent bite/scratch from rat, mouse, or squirrel; ingestion of food/water contaminated with rat excrement	Headaches, myalgias, polyarthritis, maculopapular/morbilliform/petechial/vesicular/pustular rash over palms, soles, and extremities
Relapsing fever (*Borrelia recurrentis*)	Poverty/crowding/poor sanitation (louse-borne); camping in the Grand Canyon (tick-borne)	High fever with rigors, headache, delirium, arthralgias, myalgias, hepatosplenomegaly
Rocky Mountain spotted fever	Outdoor activity in South Atlantic or southeastern US; *Dermacentor* tick bites	Headache, petechial rash on extremities, palms, and soles
Tuberculosis	Contact with TB; immigration from endemic country; homeless shelter or healthcare facility exposure	Night sweats, weight loss, atypical pneumonia, cavitary pulmonary lesions
Tularemia	Bites from *Amblyomma* or *Dermacentor* ticks, deer flies, or mosquitoes; direct contact with rabbits, squirrels, deer, raccoons, cattle, sheep, or swine	Ulcerated skin lesion at bite site, pneumonia, relative bradycardia, lymphadenopathy, conjunctivitis
Whipple's disease (*Tropheryma whipplei*)	Potential association with exposure to sewage	Chronic diarrhea, arthralgia, weight loss, malabsorption, malnutrition

Bone marrow biopsy

- **Diagnostic yield:** ~25% in two case series; especially valuable for:
  - Granulomatous infections (TB, histoplasmosis, sarcoidosis)
  - Hematologic malignancies (leukemia, lymphoma)
  - Patients with abnormal CBC (anemia, thrombocytopenia, leukopenia)
- **Organisms identified:**
  - *Mycobacterium tuberculosis*
  - Fungi (*Histoplasma*, *Cryptococcus*, *Coccidioides*)
  - Intracellular bacteria (*Brucella*, *Bartonella*)
- **Consider:** When fever pattern and presentation suggest granulomatous disease or hematologic malignancy



Imaging studies



Generally low diagnostic yield without localizing symptoms

- CT of abdomen and chest
- Ultrasound of gallbladder and hepatobiliary systems
- CT pulmonary angiogram (for pulmonary embolis)
- MRI for CNS, spleen, lymph nodes, aorta (vasculitis)
- Indium 111-tagged white blood cell scan (becoming less common)
- Gallium-67 scan (largely replaced by PET-CT)
- **PET-CT:** Superior sensitivity for inflammatory and malignant processes

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

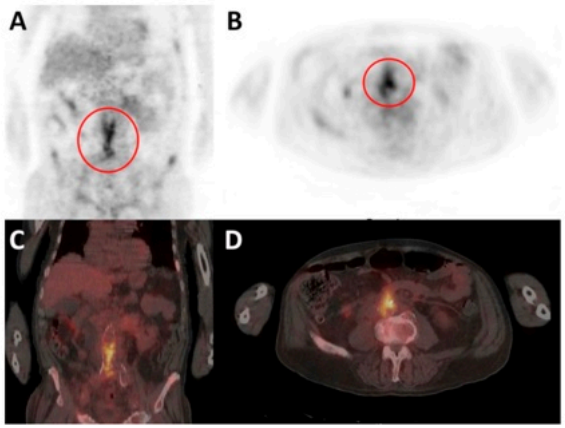


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Figure 2. A 75-year-old man, with a medical history of an aortic vascular prosthesis due to a symptomatic aneurysm and metastatic prostate carcinoma, presented with fever and night sweats. Physical examination was normal. CRP was 130 mg/L and leukocyte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

PET-CT has revolutionized the diagnostic approach to FUO. Overall sensitivities range from 86-98% and specificities from 52-85%, depending on the etiology. It is particularly useful for detecting focal sites of infection or inflammation that might be missed on conventional imaging.**Key clinical applications:** - Should be performed early in workup - Most helpful for: abscesses, osteomyelitis, vasculitis, adult-onset Still disease, Crohn disease, subacute thyroiditis - Can identify sites for targeted biopsy

Invasive diagnostic procedures

- **Biopsy techniques:**
  - Excisional biopsy (lymph node)
  - Needle biopsy (liver, kidney, muscle)
  - Laparotomy or laparoscopy for direct visualization
- **Diagnostic yield:**
  - Biopsy yields diagnosis in < 50% of cases
  - Average 2-3 biopsies needed to establish diagnosis
- **Indications:**
  - Abnormal imaging or physical exam findings
  - Lymphadenopathy suitable for lymph node biopsy
  - Suspected granulomatous disease
  - Persistent fever despite extensive workup

Treatment Section

A fundamental principle in classic FUO:

Therapy should be withheld until the cause of fever is determined

This is easier said than done in clinical practice, but the principle remains sound. Non-specific treatment with antipyretics, antibiotics, or corticosteroids

Diagnostic summary and approach

Adapted from Cunha et al. © 2020 JHU/AAM

When is immediate treatment indicated?

- **Suspected temporal arteritis**
  - Empirical corticosteroids to prevent vascular complications (blindness, stroke)
  - Do not wait for biopsy confirmation if clinical suspicion high
- **Febrile neutropenia or severe immunocompromise**
  - High prevalence of serious bacterial infections
  - Broad-spectrum antimicrobial therapy with anti-pseudomonas coverage after appropriate cultures obtained
  - No delay for culture results
- **Select cases with strong clinical suspicion:**
  - Anti-mycobacterial therapy in suspected TB (especially if respiratory symptoms)
  - Targeted therapy based on epidemiology and presentation

Prognosis

- **Determined by:** The underlying cause of fever and nature of underlying disease(s)
- **Poor prognosis:** Elderly patients with malignant neoplasms
- **Diagnostic delay worsens prognosis in:**
  - Intra-abdominal infections (perforation, sepsis)
  - Miliary tuberculosis
  - Disseminated fungal infections
  - Recurrent pulmonary emboli
- **Favorable outlook:** Patients with undiagnosed FUO after extensive evaluation
  - Most experience resolution of fever within 4 weeks without sequelae
  - **5-year mortality rate: 3.2%** for undiagnosed FUO
  - Superior to patients with diagnosed malignancy as the underlying cause

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