PART I

Clinical syndromes: general

1. Fever of unknown origin (FUO)

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OVERVIEW

Fever of unknown origin (FUO) describes prolonged fevers >101°F lasting for 3 or more weeks that remain undiagnosed after a focused FUO outpatient/inpatient workup. The causes of FUO include infectious and noninfectious disorders. A variety of infectious, malignant, rheumatic/inflammatory disorders may be associated with prolonged fevers, but relatively few persist undiagnosed for sufficient duration to be classified as FUOs.

CAUSES OF FUO

The distribution of disorders causing FUOs is dependent on age, demographics, family history, zoonotic exposures, and previous/current conditions, e.g., malignancies, rheumatic/inflammatory disorders, cirrhosis. Each category of FUO may also be approached by subgroups, e.g., elderly, immunosuppressed, transplants, febrile neutropenia, zoonoses, HIV, nosocomial, returning travelers. The differential diagnosis in each subgroup reflects the relative distribution of disorders within the subgroup, and the geographic distribution of endemic diseases. The relative distribution of causes of FUO has changed over time but, with few exceptions, the disorders responsible for FUOs have remained relatively constant over time (Table 1.1).

DIAGNOSTIC APPROACH TO FUOs

In patients presenting with prolonged fevers, the clinician should first determine if the patient indeed has an FUO. Because there are many causes of FUO, there is no "cookbook or algorithmic approach" for diagnosing FUOs. In medicine, the history provides important initial diagnostic clues and a general sense of the likely FUO category, e.g., weight loss with early anorexia suggests malignancy, arthralgias/myalgias suggest a rheumatic/inflammatory disorder, and fever with chills suggests an infectious etiology.

After an FUO category is suggested by historical clues, the physical examination should focus on history relevant findings in the differential diagnosis. The physical examination should not be comprehensive but more importantly should be carefully focused on demonstrating the presence or absence of key findings in the differential diagnosis, e.g., a complete neurologic exam is unhelpful in an FUO patient with probable adult Still's disease. On physical examination particular attention should be given to eye findings, liver, spleen, lymph nodes, joint findings, and skin lesions (Table 1.2). At this point, based upon the presence or absence of history and physical examination clues, the initial FUO diagnostic workup, e.g., nonspecific laboratory tests, should also be focused on ruling in or ruling out the most likely diagnostic possibilities. Since the patient has already been seen by one or more physicians prior to presentation, routine laboratory tests have already been done, e.g., CBC, liver function test (LFTs), urinalysis (UA), but these tests should be carefully re-reviewed for diagnostic clues, e.g., relative lymphopenia.

The "shot gun" approach to laboratory testing for FUOs should be avoided. Since the number of FUO causes are legion, it is not clinically or cost-effective to test for every cause of FUO. When asked why he robbed banks, Willy Sutton replied, "Because that's where the money is!" Similarly, a focused FUO workup should be directed at the most likely, not all, diagnostic possibilities, as suggested by the history, physical, and nonspecific laboratory tests. Nondirected testing often provides misleading information. It makes no sense to obtain thyroid function tests (TFTs) in FUOs with joint symptoms; neither should TFTs be obtained in FUOs likely due to adult Still's disease, giant cell arteritis/temporal arteritis (GCA/TA), or periarteritis nodosa (PAN).

Blood cultures should not be obtained in all cases of FUO. If the FUO differential diagnosis

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Table 1.1 Classic causes of fever of unknown origin (FUO)

Type of disorder	Common	Uncommon	Rare
Malignancy/neoplastic disorders	Lymphoma[a] Hypernephromas/renal cell carcinoma (RCC)	Pre-leukemias (AML)[a] Myeloproliferative disorders (MPDs)	Atrial myxomas Multiple myeloma Colon carcinoma Pancreatic carcinoma CNS metastases Hepatomas Liver metastases
Infectious diseases	Miliary TB SBE Brucellosis[a] Q fever[a]	Intra-abdominal/pelvic abscess Intra/perinephric abscess Typhoid fever/enteric fevers[a] Toxoplasmosis Cat scratch disease (CSD)[a] EBV CMV HIV Extrapulmonary TB (renal TB, CNS TB)	Periapical dental abscess Chronic sinusitis/mastoiditis Subacute vertebral osteomyelitis Aortoenteric fistula Relapsing fever[a] Rat-bite fever[a] Leptospirosis[a] Histoplasmosis Coccidiomycosis Visceral leishmaniasis (kala-azar) LGV Whipple's disease[a] Castleman's disease[a] (MCD) Malaria Babesiosis Ehrlichiosis
Rheumatologic/inflammatory disorders	Adult Still's disease[a] Giant cell arteritis (GCA)/temporal arteritis (TA)[a]	PAN/MPA[a] Late-onset rheumatoid arthritis (LORA)[a] SLE[a]	Takayasu's arteritis[a] Kikuchi's disease[a] Sarcoidosis (CNS) Felty's syndrome Gaucher's disease Polyarticular gout[a] Pseudogout[a] Schnitzler's syndrome[a] Behçet's disease[a] FAPA syndrome[a] (Marshall's syndrome)
Miscellaneous disorders	Drug fever[a] Alcoholic cirrhosis[a]	Subacute thyroiditis[a] Regional enteritis (Crohn's disease)[a]	Pulmonary emboli (small/multiple) Pseudolymphomas Kikuchi's disease[a] Rosai–Dorman disease[a] Erdheim–Chester disease (ECD)[a] Cyclic neutropenia[a] Familial periodic fever syndromes[a] • FMF • Hyper IgD syndrome[a] • TNF receptor-1-associated periodic syndrome (TRAPS) • Muckle–Wells syndrome Systemic mastocytosis Hypothalamic dysfunction Hypertriglyceridemia Factitious fever[a]

[a] Also cause of recurrent FUOs.

Disorders with FUO potential include any not easily diagnosed disorder with prolonged fevers, travel-related infections with prolonged fevers presenting in nonendemic areas, any relapsing/recurrent disorder with prolonged fevers, or any disorder with prolonged fevers with unusual clinical findings.

Abbreviations: CNS = central nervous system; TB = tuberculosis; SBE = subacute bacterial endocarditis; CMV = cytomegalovirus; HIV = human immunodeficiency virus; EBV = Epstein–Barr virus; LGV = lymphogranuloma venereum; PAN = periarteritis nodosa; MPA = microscopic polyangiitis; SLE = systemic lupus erythematosus; FMF = familial Mediterranean fever; MCD = multicentric Castleman's disease; FAPA = fever, aphthous ulcers, pharyngitis, adenitis; TNF = tumor necrosis factor; AML = acute myelogenous leukemia.

Adapted from: Cunha BA. Fever of unknown origin (FUO). In: Gorbach SL, Bartlett JB, Blacklow NR (Eds.) *Infectious Diseases in Medicine and Surgery.* (3rd edn.) Philadelphia: WB Saunders, 2004; pp. 1568–1577 and Cunha BA. Overview. In: Cunha BA (Ed.) *Fever of Unknown Origin.* New York: Informa Healthcare; 2007; pp. 1–16.

Table 1.2 History and physical examination clues to fever of unknown origin (FUO) categories

	Historical features		Clues from the history	Physical examination findings		Clues from the physical examination
Malignant/ neoplastic disorders	• PMH/FMH malignancy	→	Possibility of same disease likely	• Fever pattern:		
	• HA/mental confusion	→	CNS metastases, lymphomas, multiple myeloma, atrial myxoma (CNS emboli)	Relative bradycardia Hectic/septic fevers (Pel-Ebstein)	→ →	CNS, malignancies, lymphomas Lymphomas
	• Weight loss (with early decreased appetite)	→	Any malignant/neoplastic disorder	• Cranial nerve palsies	→	CNS lymphomas, CNS neoplasms
	• Early satiety	→	Lymphomas, any malignant/neoplastic disorder causing splenomegaly	• Fundi: Roth spots • Fundi: cytoid bodies (cotton wool spots)	→ →	Lymphomas, atrial myxoma Atrial myxoma
	• Pruritus (post hot shower/bath)	→	Lymphoma, MPDs	• Fundi: retinal hemorrhages	→	Pre-leukemia (AML)
	• Night sweats	→	Any malignant/neoplastic disorder	• Adenopathy	→	Lymphoma, Kikuchi's disease, Rosai–Dorfman disease
	• Abdominal discomfort/pain	→	Hypernephroma, hepatoma, liver metastases, colon carcinoma, pancreatic carcinoma	• Sternal tenderness • Heart murmur	→ →	Pre-leukemia (AML), MPDs Marantic endocarditis, atrial myxoma
	• Testicular pain	→	Lymphoma	• Hepatomegaly	→	Hepatoma, hypernephroma, liver metastases
	• Bone pain	→	Multiple myeloma, any malignant/ neoplastic disorder with bone involvement	• Splenomegaly • Splinter hemorrhages • Epididymitis	→ → →	Lymphomas, MPDs Atrial myxoma Lymphomas
Infectious diseases	• PMH/FMH of infections	→	Possibility of same disease high	• Fever pattern:		
	• HA/mental confusion	→	Brucellosis, CSD, ehrlichiosis, Q fever, malaria, leptospirosis, Whipple's disease, typhoid fever/enteric fevers, rat-bite fever, relapsing fever, CNS TB, HIV, LGV	Relative bradycardia Double quotidian fever Camelback fever curve	→ → →	Typhoid fever/enteric fevers, leptospirosis, Q fever, malaria, babesiosis, ehrlichiosis Visceral leishmaniasis (kala-azar) Ehrlichiosis, leptospirosis, brucellosis, rat-bite fever (*S. minus*)
	• Recent/similar illness exposure	→	Possibility of same disease high	Morning temperature spikes	→	Miliary TB, typhoid fever/enteric fevers
	• Surgical/invasive procedures	→	Abscess, SBE			
	• Aortic aneurysm/ repair	→	Q fever, enteric fever	Relapsing fevers	→	Brucellosis, malaria, rat-bite fever (*S. moniliformis*)
	• STD history	→	LGV	• Abducens (CN VI) palsy	→	CNS TB
	• Recent travel	→	Typhoid/enteric fevers, leptospirosis, malaria, visceral leishmaniasis (kala-azar), brucellosis, Q fever	• Conjunctival suffusion • Conjunctival hemorrhages	→ →	Trichinosis, relapsing fever, leptospirosis SBE
	• Insect exposure	→	Malaria, ehrlichiosis, babesiosis, visceral leishmaniasis (kala-azar), relapsing fever	• Chorioretinitis • Choroid tubercles	→ →	Toxoplasmosis, TB, histoplasmosis Miliary TB
	• Pet/animal contact	→	Q fever, CSD, toxoplasmosis, rat-bite fever, relapsing fever, leptospirosis, brucellosis	• Roth spots • Palatal petechiae	→ →	SBE EBV, CMV, toxoplasmosis
	• Unpasteurized milk/ cheese consumption	→	Q fever, brucellosis	• Tongue ulcer • Adenopathy	→ →	Histoplasmosis CSD, EBV, CMV

	Historical features		Clues from the history	Physical examination findings		Clues from the physical examination
	• Undercooked meat consumption	→	Toxoplasmosis, trichinosis	• Heart murmur	→	SBE
				• Spinal tenderness	→	Subacute vertebral osteomyelitis, typhoid fever/enteric fever, skeletal TB, brucellosis
	• Blood transfusions	→	Malaria, babesiosis, ehrlichiosis, CMV, HIV	• Hepatomegaly	→	Q fever, typhoid fever/enteric fevers, brucellosis, visceral leishmaniasis (kala-azar), rat-bite fever, relapsing fever
	• Poor dentition	→	SBE, apical root abscess			
	• Sleep disturbances	→	Brucellosis, relapsing fever, leptospirosis	• Splenomegaly	→	Miliary TB, EBV, CMV, typhoid fever/enteric fevers, brucellosis, histoplasmosis, ehrlichiosis, malaria, Q fever, SBE, CSD Rat-bite fever, relapsing fever
	• Early satiety	→	EBV, CMV, Q fever, brucellosis, SBE, miliary TB			
	• Arthralgias	→	Rat-bite fever, LGV, Whipple's disease, brucellosis	• Splinter hemorrhages	→	SBE
				• Ostler's nodes/ Janeway lesions	→	SBE
	• Myalgias	→	Q fever, leptospirosis, relapsing fever, trichinosis	• Skin hyperpigmentation	→	Visceral leishmaniasis (kala-azar), Whipple's disease
	• Sinusitis	→	Chronic sinusitis			
	• Night sweats	→	Miliary TB, histoplasmosis	• Epididymitis	→	EBV, renal TB, brucellosis
	• Weight loss	→	Miliary TB, histoplasmosis			
	• Tongue pain	→	Histoplasmosis, relapsing fever			
	• Neck pain	→	Subacute vertebral osteomyelitis, chronic mastoiditis			
	• Tender finger tips	→	SBE			
	• Abdominal pain	→	Relapsing fever, leptospirosisv, typhoid fever/enteric fevers, trichinosis			
	• Back pain	→	Subacute vertebral osteomyelitis, brucellosis, SBE			
	• Testicular pain	→	EBV			
Rheumatic/ inflammatory disorders	• PMH/FMH of rheumatic disorders	→	Possibility of the same disease likely	• Fever pattern:		
	• HA/mental confusion	→	GCA/TA, CNS sarcoidosis, adult Still's disease	Double quotidian fever	→	Adult Still's disease
				Morning temperature spikes	→	PAN
	• Transient facial edema	→	Takayasu's arteritis			
	• Hearing loss	→	PAN	• Lacrimal gland enlargement	→	LORA, sarcoidosis, SLE
	• Nasal stuffiness	→	Sarcoidosis	• Parotid gland enlargement	→	Sarcoidosis
	• Joint pain/swelling	→	SLE, LORA, sarcoidosis, adult Still's disease	• Rash	→	Sarcoidosis, SLE, adult Still's disease
				• Unequal pulses	→	Takayasu's arteritis
	• Eye symptoms	→	PAN, sarcoidosis	• Conjunctival nodules	→	Sarcoidosis
	• Transient blindness	→	PAN, SLE, GCA/TA, Takayasu's arteritis	• Dry eyes	→	Sarcoidosis
	• Neck/jaw pain	→	GCA/TA, Takayasu's arteritis	• Watery eyes	→	PAN
	• Sore throat	→	SLE, adult Still's disease	• Argyll-Robertson or Adies' pupils	→	Sarcoidosis
	• Tongue tenderness	→	GCA/TA	• Band keratopathy	→	Adult Still's disease, sarcoidosis
	• Mouth ulcers	→	SLE	• Episcleritis	→	GCA/TA, LORA, PAN
	• Night sweats	→	Takayasu's arteritis	• Scleritis	→	SLE
	• Rash	→	Adult Still's disease, SLE, sarcoidosis	• Iritis	→	Adult Still's disease, SLE, sarcoidosis

Table 1.2 *(continued)*

	Historical features		Clues from the history	Physical examination findings		Clues from the physical examination
	• Dry cough	→	Sarcoidosis, GCA/TA	• Uveitis	→	Adult Still's disease, SLE, LORA, sarcoidosis
	• Acalculous cholecystitis	→	SLE	• Fundi: optic neuritis with "macular star"	→	PAN
	• Intermittent abdominal pain	→	SLE, PAN, adult Still's disease			
	• Tender finger tips	→	SLE, PAN			
	• Testicular pain	→	PAN, SLE			
				• Fundi: cytoid bodies (cotton wool spots)	→	SLE, GCA/TA, PAN, adult Still's disease
				• Fundi: "candlewax drippings"	→	Sarcoidosis
				• Fundi: Roth spots	→	SLE, PAN
				• Fundi: central/branch retinal artery occlusion	→	SLE, GCA/TA, Takayasu's arteritis
				• Fundi: central retinal vein occlusion	→	SLE, sarcoidosis
				• Oral ulcers	→	SLE, Behçet's disease, FAPA syndrome
				• Tongue ulcers	→	GCA/TA
				• Adenopathy	→	SLE, LORA, sarcoidosis
				• Splenomegaly	→	Felty's syndrome, SLE, adult Still's disease, sarcoidosis
				• Heart murmur	→	SLE (Libman–Sacks)
				• Arthritis/joint effusion	→	Any rheumatic/inflammatory disorder
				• Epididymitis	→	PAN, SLE, sarcoidosis
Miscellaneous disorders	• Negative HPI/PMH for infectious, rheumatic/inflammatory, malignant/neoplastic disorders	→	Non-miscellaneous disorders unlikely	• Fever pattern: Relative bradycardia	→	Drug fever, factitious fever
	• PMH of periodic fevers (FMF, hyper IgD syndrome, TRAPS, Muckle–Wells syndrome)	→	Possibility of same disease likely	• Periorbital edema	→	TRAPS
				• Parotid enlargement	→	Alcoholic cirrhosis
				• Episcleritis	→	Regional enteritis (Crohn's disease)
	• Drugs/medications	→	Drug fever, pseudolymphoma	• Fundi: lipemia retinalis	→	Hypertriglyceridemia
	• Fume exposure	→	Fume fever	• Oral ulcers	→	Hyper IgD syndrome
	• Alcoholism	→	Alcoholic cirrhosis	• Adenopathy	→	Pseudolymphoma, hyper IgD syndrome (cervical), Schnitzler's syndrome (axillary/inguinal)
	• Regional enteritis (Crohn's disease)	→	Abscess	• Signs of alcoholic cirrhosis	→	Alcoholic cirrhosis
	• Thyroid disease	→	Subacute thyroiditis	• Hepatomegaly	→	Schnitzler's syndrome, hyper IgD syndrome
	• Hyperlipidemia	→	Hypertriglyceridemia			
	• Medical personnel	→	Factitious fever	• Splenomegaly	→	Regional enteritis (Crohn's disease), alcoholic cirrhosis, FMF, hyper IgD syndrome, Muckle–Wells syndrome, Schnitzler's syndrome
	• Sore throat	→	Subacute thyroiditis, hyper IgD syndrome			
	• Neck/jaw pain	→	Subacute thyroiditis	• Epididymitis	→	FMF, TRAPS
	• Intermittent abdominal pain	→	Regional enteritis (Crohn's disease), FMF, Muckle–Wells syndrome	• Perirectal fistula	→	Regional enteritis (Crohn's disease)

Historical features		Clues from the history	Physical examination findings	Clues from the physical examination
• Arthralgias/joint pains	→	FMF, hyper IgD syndrome, TRAPS, Muckle–Wells syndrome, cyclic neutropenia, Schnitzler's syndrome		
• Testicular pain	→	FMF, TRAPS		
• Bone pain	→	Schnitzler's syndrome		
• Intermittent urticaria	→	Schnitzler's syndrome Hyper IgD syndrome		

Abbreviations: PMH = past medical history; FMH = family medical history; HA = headache; CMV = cytomegalovirus; EBV = Epstein–Barr virus; ESR = erythrocyte sedimentation rate; PAN = periarteritis nodosa;
MPA = microscopic polyangiitis; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus; TB = tuberculosis;
MPDs = myeloproliferative disorders; LORA = late-onset rheumatoid arthritis; RCC = renal cell carcinoma; GCA = giant cell arteritis;
TA = temporal arteritis; AML = acute monocytic leukemia; HIV = human immunodeficiency virus; CNS = central nervous system;
CSD = cat scratch disease; FMF = familial Mediterranean fever; TRAPS = tartrate-resistant acid phosphatase; LGV = lymphogranuloma venereum; STD = sexually transmitted disease; CN VI = cranial nerve VI; FAPA = fever, aphthous ulcers, pharyngitis, adenitis.
Adapted from Cunha CB. Infectious disease differential diagnosis. In: Cunha BA, ed. *Antibiotic Essentials* 12th edn.;
Jones & Bartlett, Sudbury, MA, 2013; pp. 475–506 and Cunha BA. Nonspecific tests in the diagnosis of fever of unknown origin. In: Cunha BA, ed. *Fever of Unknown Origin*. New York: Informa Healthcare; 2007; pp. 151–158.

includes adult Still's disease, subacute thyroiditis, or GCA/TA, blood cultures make little sense. Even if an infectious etiology is likely, blood cultures should not always be obtained, e.g., Epstein–Barr virus (EBV), cytomegalovirus (CMV), HIV. Blood cultures are ordered to rule out subacute bacterial endocarditis (SBE). The diagnosis of SBE is based on an otherwise unexplained high-grade/continuous bacteremia (with a known endocarditis pathogen) *plus* a cardiac vegetation. The diagnosis of culture-negative endocarditis (CNE) is not based on the presence of negative blood cultures and a vegetation. Rather, the diagnosis of CNE is based on three essential key findings, i.e., a cardiac vegetation, negative blood cultures *plus* peripheral signs of SBE. The differential diagnosis of CNE includes marantic endocarditis (usually due to a malignancy). The diagnosis of marantic endocarditis is based on the size/shape of vegetation (different from SBE vegetations). Alternately, if an infectious etiology of CNE is suspected, then serologic tests for brucella and Q fever should be obtained. While brucella SBE vegetations are easily seen, Q fever SBE vegetations may be small or undetectable.

Because the appropriateness of therapy is based on a correct diagnosis, the main focus of the clinical approach to FUOs is diagnostic rather than therapeutic. The diagnostic workup should be focused based on signs, symptoms, and non specific laboratory abnormalities, which may either enhance or diminish particular diagnostic possibilities. Nonspecific laboratory tests often provide important albeit often subtle clues in the FUO workup. By definition nonspecific laboratory tests are nonspecific, but when considered in concert often are helpful in narrowing diagnostic possibilities and in prompting specific diagnostic testing to rule in or rule out the most likely diagnoses being considered. Importantly, the diagnostic workup should not be excessive and should not include every conceivable cause of FUO. Focused diagnostic testing should be based on the pertinent aspects of the history, the presence or absence of characteristic physical findings, and a presumptive syndromic diagnosis based on combining key nonspecific laboratory findings.

NONSPECIFIC LABORATORY TEST CLUES

Nonspecific laboratory clues are important in focusing the FUO diagnostic workup. In addition to the initial history and physical examination, selected nonspecific laboratory tests are helpful. If malignancy is a likely cause of an FUO, highly elevated ferritin, LDH, or B_{12} levels often point to an occult malignancy. Serum protein electrophoresis (SPEP) is helpful in demonstrating monoclonal or polyclonal gammopathy which may be a clue to specific disorders. As with all laboratory tests, nonspecific findings should be interpreted in the appropriate clinical context, e.g., an FUO

Table 1.3 FUO nonspecific: laboratory tests

Nonspecific tests for FUOs
• CBC
• ESR
• LFTs
• Ferritin
• SPEP
• UA
CBC
• Leukocytosis [a] → malignant/neoplastic and infectious focused workup
• Leukopenia [a] → malignant/neoplastic, infectious, and rheumatic inflammatory focused workup
• Anemia [a] → malignant /neoplastic, infectious, and rheumatic/inflammatory focused workup
• Myelocytes/metamyelocytes [a] → malignant/neoplastic focused workup
• Lymphocytosis [a] → malignant/neoplastic and infectious focused workup
• Lymphopenia [a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup
• Atypical lymphocytes [a] → infectious and malignant/neoplastic focused workup
• Eosinophilia[a] → malignant/neoplastic, rheumatic/inflammatory, and infectious focused workup
• Basophilia[a] → malignant/neoplastic focused workup
• Thrombocytosis [a] → malignant/neoplastic, infectious, and rheumatic inflammatory focused workup
• Thrombocytopenia [a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup
ESR
• Highly elevated [a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup
LFTs
• Elevated SGOT/SGPT [a] → infectious and rheumatic/inflammatory focused workup
• Elevated alkaline phosphatase [a] → malignant/neoplastic and rheumatic/inflammatory focused workup
Ferritin
• Highly elevated [a] → malignant/neoplastic, rheumatic/inflammatory, and miscellaneous disorders focused workup
SPEP
• Monoclonal gammopathy → malignant/neoplastic and miscellaneous disorders workup
• Polyclonal gammopathy → infectious rheumatic/inflammatory and miscellaneous disorders focused workup
UA
• Microscopic hematuria → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup[a]

[a]See Table 1.4.

Abbreviations: CBC = complete blood count; ESR = erythrocyte sedimentation rate; LFTs = liver function tests; UA = urine analysis; RD = rheumatic disease; SGOT/SGPT = serum glutamic-oxaloacetic transaminase/serum glutamic pyruvate transaminase; SPEP = serum protein electrophoresis.

Adapted from Cunha BA. A focused diagnostic approach. In: Cunha BA (Ed.) *Fever of Unknown Origin*. New York. Informa Healthcare; 2007; pp. 9–16 and Cunha, BA. Fever of unknown origin: focused diagnostic approach based on clinical clues from the history, physical examination, and laboratory tests. *Infect Dis Clin North Am* 2007;21:1137–1187.

with polyclonal gammopathy, heart murmur, negative blood cultures, and peripheral signs of endocarditis, and should suggest an atrial myxoma. In an adult with FUO, otherwise unexplained highly elevated serum ferritin levels should suggest either a neoplasm/malignancy, myeloproliferative disorder (MPD), or a rheumatic/inflammatory disorder. Elevated serum ferritin levels are also present in systemic lupus erythematosus (SLE) flares, adult Still's disease, and GCA/TA. Elevated ferritin levels also have exclusionary diagnostic importance in FUOs, e.g., malignancy is less likely with unelevated/minimally elevated serum ferritin levels (Tables 1.3, 1.4, and 1.5).

THERAPEUTIC CONSIDERATIONS

The clinical approach to FUO is based on making a correct diagnosis. Empiric therapy is rarely justifiable unless a potentially treatable life-threatening disease is a definite/highly probable diagnosis. Antipyretics should be used only under unusual circumstances. Fever, per se, should not be treated, as treatment eliminates a potentially important diagnostic sign, i.e., the fever curve. Temperature/pulse relationships may also have important diagnostic implications, i.e., relative bradycardia. With an FUO if the differential diagnosis is between malignancy and infection, the Naprosyn test (naproxen

Table 1.4 FUO: nonspecific laboratory clues

Leukopenia
- Miliary TB
- Lymphomas
- Pre-leukemia (AML)
- Typhoid fever/enteric fevers
- Felty's syndrome
- Gaucher's disease

Monocytosis
- Miliary TB
- Histoplasmosis
- PAN/MPA
- GCA/TA
- LORA
- SLE
- Sarcoidosis
- CMV
- Brucellosis
- SBE
- Lymphomas
- Carcinomas
- MPDs
- Regional enteritis (Crohn's disease)
- Gaucher's disease

Eosinophilia
- Trichinosis
- Lymphomas
- Hypernephroma (RCC)
- PAN/MPA
- Kikuchi's disease
- Drug fever

Basophilia
- Carcinomas
- Lymphomas
- Pre-leukemia (AML)
- MPDs

Lymphocytosis
- Miliary TB
- Histoplasmosis
- Typhoid fever/enteric fevers
- Brucellosis
- EBV
- CMV
- Toxoplasmosis
- Visceral leishmaniasis (kala-azar)
- Lymphomas

Relative lymphopenia
- Q fever
- Brucellosis
- Whipple's disease
- Miliary TB
- Histoplasmosis
- Malaria
- Babesiosis
- Ehrlichiosis
- EBV
- CMV
- SLE
- Lymphomas

Atypical lymphocytes
- Malaria
- Babesiosis
- Ehrlichiosis
- EBV
- CMV
- Toxoplasmosis
- Brucellosis
- Kikuchi's disease
- Drug fever

Thrombocytosis
- SBE
- Q fever
- Miliary TB
- Histoplasmosis
- Subacute vertebral osteomyelitis
- Carcinomas
- Lymphomas
- Hypernephroma (RCC)
- MPDs
- PAN/MPA
- GCA/TA

Thrombocytopenia
- Leukemias
- Lymphomas
- MPDs
- Multiple myeloma
- EBV
- CMV
- Alcoholic cirrhosis
- Drug fever
- PAN/MPA
- SLE
- Malaria
- Babesiosis
- Ehrlichiosis
- Brucellosis
- Relapsing fever
- Miliary TB
- Histoplasmosis
- Visceral leishmaniasis (kala-azar)
- Ehrlichiosis

Rheumatoid factors
- SBE
- Visceral leishmaniasis (kala-azar)
- LORA
- Sarcoidosis
- SLE
- Alcoholic cirrhosis

Elevated alkaline phosphatase
- Hepatoma
- Miliary TB
- Lymphomas
- GCA/TA
- Gaucher's disease
- Systemic mastocytosis
- Schnitzler's syndrome

ESR (>100 mm/hr)
- SBE
- Abscesses
- Subacute vertebral osteomyelitis
- Hypernephroma (RCC)
- Carcinomas
- Lymphomas
- MPDs
- Atrial myxoma
- PAN/MPA
- Takayasu's arteritis
- Hyper IgD syndrome
- Erdheim–Chester disease (ECD)
- Rosai–Dorman disease
- Kikuchi's disease
- Schnitzler's syndrome
- Castleman's disease (MCD)
- Adult Still's disease
- GCA/TA
- LORA
- Drug fever

SPEP

Polyclonal gammopathy
- HIV
- CMV
- Alcoholic cirrhosis
- Castleman's disease (MCD)

Monoclonal gammopathy
- Multiple myeloma
- Hyper IgD syndrome
- Schnitzler's syndrome (IgM > IgG)
- Castleman's disease (MCD)

Elevated α_1/α_2 globulins
- Lymphoma
- SLE

Elevated serum transaminases
- EBV
- CMV
- Typhoid fever/enteric fevers
- Brucellosis
- Q fever
- Malaria
- Babesiosis
- Ehrlichiosis
- Adult Still's disease
- Kikuchi's disease
- Drug fever

Microscopic hematuria
- SBE
- Renal TB
- Brucellosis
- PAN/MPA
- Lymphomas
- Hypernephroma (RCC)

Multiple myeloma	Erdheim–Chester disease (ECD)
Alcoholic cirrhosis	Adult Still's disease
LORA	GCA/TA
Whipple's disease	PAN/MPA
Typhoid fever/enteric fevers	Hypernephroma (RCC)
	Liver metastases
	Subacute thyroiditis
	Elevated serum ferritin
	Malignancies
	Pre-leukemia (AML)
	MPDs
	Rosai–Dorfman disease
	Erdheim–Chester disease (ECD)
	SLE (flare)
	GCA/TA
	LORA
	Adult Still's disease
	Subacute thyroiditis

Abbreviations: CMV = cytomegalovirus; EBV = Epstein–Barr virus; ESR = erythrocyte sedimentation rate; PAN = periarteritis nodosa; MPA = microscopic polyangiitis; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus; TB = tuberculosis; MPDs = myeloproliferative disorders; LORA = late-onset rheumatoid arthritis; RCC = renal cell carcinoma; GCA = giant cell arteritis; TA = temporal arteritis; AML = acute monocytic leukemia; HIV = human immunodeficiency virus; MCD = multicentric Castleman's disease.

Adapted from Cunha CB. Infectious disease differential diagnosis. In: Cunha BA (Ed.) *Antibiotic Essentials* (12th edn.). Jones & Bartlett, Sudbury, MA; 2013; pp. 475–506 and Cunha BA. Nonspecific tests in the diagnosis of fever of unknown origin. In: Cunha BA (Ed.) *Fever of Unknown Origin*. New York: Informa Healthcare; 2007; pp. 151–158.

Table 1.5 FUO: sign and symptom focused testing

FUO infectious disease tests	FUO neoplastic disease tests	FUO rheumatic/inflammatory tests	Miscellaneous other tests
Blood tests (if suspected by history and physical examination)			
• Q fever IgM/IgG titers • Brucella IgM/IgG titers • Bartonella IgM/IgG titers • Salmonella IgM/IgG titers • EBV IgM/IgG titers • CMV IgM/IgG titers • HHV-8 IgM/IgG titers • **Blood cultures**	• Ferritin • LDH • B_{12} levels • β-2 microglobulin levels • ACE† • SPEP	• RF • ANA • DsDNA • Ferritin • CPK • ACE • Anti-CCP • Antiphospholipid antibodies • SPEP	• **TFTs** (thyroid function tests) and **ATAs** (anti-thyroid antibody tests) If subacute thyroiditis suspected • **GGTP** • **B_{12} levels** If alcoholic cirrhosis suspected • **MEFV gene studies** If FMF suspected
If PVE suspected or if peripheral signs of SBE present *and* TTE/TEE shows a vegetation **Culture-negative endocarditis (CNE)** TTE shows a vegetation *plus* negative blood cultures *plus* peripheral signs of SBE present **Infectious CNE** If vegetation on TTE/TEE *and* blood cultures are negative, *and* peripheral signs of SBE present → proceed with *infectious CNE workup* (Q fever, etc.) **Noninfectious CNE (marantic endocarditis)** If *infectious CNE workup negative* → proceed with marantic endocarditis workup (malignancy, lymphoma, etc.)			