Fever of Unknown Origin (FUO) Clinical Presentation

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Author: Sandra G Gompf, MD, FACP, FIDSA; Chief Editor: Michael Stuart Bronze, MD

Sandra G Gompf, MD, FACP, FIDSA Associate Professor of Infectious Diseases and International Medicine, University of South Florida College of Medicine; Chief, Infectious Diseases Section, Director, Occupational Health and Infection Control Programs, James A Haley Veterans Hospital

Sandra G Gompf, MD, FACP, FIDSA is a member of the following medical societies: American College of Physicians, Infectious Diseases Society of America

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Chief Editor

Michael Stuart Bronze, MD David Ross Boyd Professor and Chairman, Department of Medicine, Stewart G Wolf Endowed Chair in Internal Medicine, Department of Medicine, University of Oklahoma Health Science Center; Master of the American College of Physicians; Fellow, Infectious Diseases Society of America
Background

The syndrome of fever of unknown origin (FUO) was defined in 1961 by Petersdorf and Beeson as the following: (1) a temperature greater than 38.3°C (101°F) on several occasions, (2) more than 3 weeks’ duration of illness, and (3) failure to reach a diagnosis despite one week of inpatient investigation. [1, 2] However, it is important to allow for flexibility in this definition. The emergence of human immunodeficiency virus (HIV) and the expanding use of immunomodulating therapies prompted Durack and Street to propose differentiating FUO into four categories: classical FUO (Petersdorf definition), hospital-acquired FUO, immunocompromised or neutropenic FUO, and HIV-related FUO. [3]

Emerging techniques such as molecular diagnostics, expanding use of immunocompromising therapies and organ transplantation, and the advent of globally mobile populations demand an evolving approach to defining and evaluating FUO. [4, 3, 5] Modern imaging techniques (eg, ultrasonography, computed tomography [CT] scanning, magnetic resonance imaging [MRI], positron emission tomography [PET]) enable early detection of abscesses and solid tumors that were once difficult to diagnose.

History

The history can provide important clues to fever of unknown origin (FUO) due to zoonoses, malignancies, and inflammatory/immune disorders. In adults with FUO, inquire about symptoms involving all major organ systems and obtain a detailed history of general symptoms (eg, fever, weight loss, night sweats, headaches, rashes). Record all symptoms, even those that disappeared before the examination. Previous illnesses (including psychiatric illnesses) are important. Look for patterns of symptoms and relapsing fevers.

Make a detailed history evaluation that includes the following:

- Family history
- Immunization status
• Dental history
• Occupational history
• Travel history, especially within the prior year
• Nutrition and weight history (including consumption of dairy products); note changes in the fit of clothing if the patient does not monitor weight
• Drug history (over-the-counter medications, prescription medications, illicit substances)
• Sexual history
• Recreational habits
• Animal contacts (including possible exposure to ticks and other vectors)
• Surgery, invasive procedures, trauma

Fever pattern

Fever with rigors or shaking chills is most suggestive of infection, as opposed to noninfectious inflammatory conditions.

In general, specific fever patterns do not correlate strongly with specific diseases. Notable exceptions include classic recurrent fevers, as follows:

• Tertian fever in prolonged malaria (occurring every third day)
• Undulant fever in brucellosis (evening fevers and sweats resolving by morning)
• Tick-borne relapsing fever in borreliosis (week-long fevers with week-long remissions)
• Pel-Ebstein fever in Hodgkin disease (week-long high fevers with week-long remissions)
• Periodic fevers in cyclic neutropenia
• Double quotidian fever (two fever spikes a day) in adult Still disease; also seen in malaria, typhoid, and other infections
• Morning fevers in polyarteritis nodosa, tuberculosis, and typhoid

Historical clues to likely noninfectious inflammatory causes of FUO

Collagen vascular and autoimmune diseases can manifest as FUO if the fever precedes other, more specific manifestations (eg, arthritis, pneumonitis, renal involvement). Weight loss is not unusual.

Clues and etiologic associations are as follows:

• Headache, jaw claudication, and visual disturbances (visual loss, blurred vision, diplopia, amaurosis fugax): Giant cell or temporal arteritis
• Symmetrical pain and stiffness of lumbar spine and large proximal muscles (neck, shoulders, hips, thighs): Polymyalgia rheumatica; also myalgias, tender muscles, lacelike rash (livedo reticularis), testicular pain
• High-spiking fevers, nonpruritic morbilliform rash that follows the fever curve, arthralgias: Adult-onset Still disease, lymphadenopathy

• Facial rash: SLE

• Right lower quadrant pain, diarrhea (or none): Crohn disease (regional enteritis); Yersinia enteritis may mimic Crohn disease or appendicitis

• Erythema nodosum, painful nodules on shins: idiopathic erythema nodosum may itself cause fever sarcoidosis; Crohn disease; ulcerative colitis; Behçet disease

Historical clues to likely infectious causes of FUO

Clues and etiologic associations are as follows:

• Previous abdominal surgery, trauma, or a history of diverticulosis, peritonitis, endoscopy, urologic or gynecologic procedures: Intraabdominal abscess, perinephric abscess, psoas abscess

• Erythema nodosum, painful nodules on shins: Granulomatous fungal infections, histoplasmosis, coccidioidomycosis, Yersinia enteritis, tuberculosis

Animal and animal product exposures

A history of exposure to unpasteurized dairy (eg, swine, cattle, goats, camels, sheep) may suggest the following:

• Brucellosis

• Coxiella burnetii (chronic Q fever, Q fever endocarditis; parturient animals aerosolize Coxiella from the placenta)

• Yersinia enterocolitica/ Yersinia pseudotuberculosis: Mesenteric adenitis, pseudoappendicitis, with or without diarrhea

Exposure to birds (especially new pets, sick birds) may suggest Chlamydia psittaci infection.

Exposure to cats or cat litter may suggest toxoplasmosis or cat scratch disease (especially kittens).

Exposure to undercooked or undersmoked game meats, especially bear, cougar, wild hog, may suggest trichinosis (diffuse myalgias).

Travel-related and other environmental exposures

Travel-related and other environmental exposures are as follows:

• Desert areas of the southwest United States, California: Coccidioides immitis infection

• River valleys (Ohio, Mississippi, Central/South America): Histoplasma, Blastomyces infection

• Caves (bats): Histoplasma infection

• Swimming in rivers, fresh water, especially with rains: Leptospirosis
• Rural Central/South America, Africa, Asia: Tuberculosis, especially extrapulmonary; malaria (in malaria-prone areas; travelers of developed countries may not seek pretravel advice or take malaria prophylaxis; malaria may manifest weeks to months after return home)

• Mediterranean, tropics: Visceral leishmaniasis

• United States, rodent-infested cabins: Borrelia hermsii (tick-borne relapsing fever), week-long fevers interrupted by week-long remissions

• North America, Eurasia, tick-infested brush and forest: Borrelia miyamotoi

• Middle East, Latin America, refugees, disrupted civil services in disaster or war, humanitarian aid workers: Borrelia recurrentis/Brucella melitensis (louse-borne relapsing fever)

• Uncertain sanitation, adventurous eating: Salmonella typhi (typhoid)

Sexual encounters without barrier precautions

Travelers are especially likely to experience unanticipated encounters out of their usual norm; consider HIV, disseminated gonorrhea.

Childcare, daycare, grandchildren

Acute Epstein-Barr virus (EBV) infection is easily spread, and a small percentage of adults are not immune; fever for several weeks with or without organomegaly may be the only symptom in older adults.

Acute cytomegalovirus (CMV) is similarly easy to acquire and may cause several weeks of fever in adults (reactivation is also possible, with manifestations in several organ systems).

Historical clues to malignant causes of FUO

Historical clues to malignant causes of FUO are as follows:

• Pel-Ebstein fever in Hodgkin disease (week-long high fevers with week-long remissions)

• Lymphadenopathy, painless: Lymphoma, leukemia

• Weight loss with anorexia

• Itching after a hot bath: Lymphoma

• Erythema nodosum, painful nodules on shins: Lymphoma

Historical clues to miscellaneous causes of FUO

Historical clues to miscellaneous causes of FUO are as follows:

• Prolonged immobility, car trips, flights: Thromboembolic disease

• Ethanol abuse: Alcoholic hepatitis, cirrhosis (endotoxemia of portal circulation)

• Medication list review: Drug fever

• Anticoagulant use: Hematoma, occult hemorrhage
Practice Essentials

Key features of fever of unknown origin (FUO), also known as pyrexia of unknown origin (PUO), are as follows:

• Unexplained fevers are worrisome to patients and clinicians, but most persistent fevers are diagnosed, and often within one week of hospital evaluation or 3 outpatient visits.

• Most fevers that persist beyond this period are caused by common conditions presenting uncommonly.

• Hundreds of conditions may cause FUO. While infections remain a significant cause, most FUOs in the developed world are caused by noninfectious inflammatory disorders, with malignancy a much smaller percentage. Infection is likely to evolve with increased global travel and use of immunomodulating drugs.

• The differential diagnoses of FUO depend on and continue to evolve based on regional factors, exposures, and available diagnostic tools.

• A significant percentage of FUO cases are caused by miscellaneous conditions, and there is no standard algorithm for evaluating FUO. The approach to diagnostic study is best guided by ongoing assessment for historical, physical, and basic laboratory clues. Following clues and beginning with the least invasive evaluation avoids unnecessary harm and cost to the patient.

• Physical examination in FUO should pay special attention to skin, eyes, lymph nodes, liver, and spleen.

• It is reassuring that most cases of FUO that remain undiagnosed despite intensive evaluations have a good long-term prognosis and resolve within a year.

Physical Examination

Definitive documentation of fever and exclusion of factitious fever are essential early steps in the physical examination. Measure the fever more than once and in the presence of healthcare personnel to exclude manipulation of thermometers.

On physical examination, pay special attention to the eyes, skin, lymph nodes, spleen, heart, abdomen, and genitalia.

Repeat a regular physical examination daily while the patient is hospitalized. Pay special attention to rashes, new or changing cardiac murmurs, signs of arthritis, abdominal tenderness or rigidity, lymph node enlargement, funduscopic changes, and neurologic deficits.

Physical examination clues to causes of FUO are as follows:

• Pulse-temperature deficit or relative bradycardia (inappropriately low pulse rate for degree of fever, in the absence of beta blockade): Typhoid fever, Q fever, psittacosis, legionellosis, lymphoma, drug fever

• Unequal pulse in upper extremities: Takayasu arteritis

• Eyes - Roth spots, retinal artery occlusion: SLE, vasculitis, bacterial endocarditis, cat scratch disease (stellate retinitis)
• Oral ulcers: SLE, Behçet disease, histoplasmosis
• Tender tooth on percussion, caries/gingivitis: Dental abscess
• Enlarged or tender thyroid: Thyroiditis
• Lymphadenopathy: Sarcoidosis, SLE, adult-onset Still disease, granulomatous infections, hematologic malignancies
• Cardiac murmur: SLE (Libman-Sacks endocarditis), bacterial endocarditis
• Hepatomegaly without splenomegaly: Granulomatous hepatitis, primary liver cancer, renal cell carcinoma, or liver metastases; excludes collagen vascular disease and hematologic malignancy
• Splenomegaly without hepatomegaly: Bacterial endocarditis, EBV/CMV infection, typhoid, tuberculosis, histoplasmosis, brucellosis, malaria, Q fever, borreliosis (relapsing fevers), cirrhosis
• Tenderness to palpation of sternum: Hematologic malignancy
• Tenderness to percussion over a vertebra: Vertebral osteomyelitis, tuberculosis, typhoid, brucellosis
• Epididymitis or nodules: Sarcoid, SLE, polyarteritis nodosa
• Tender red nodules on shins: Idiopathic erythema nodosum (EN), collagen vascular disease, granulomatous infections, EBV infection, typhoid, bartonellosis, drug fever

Etiology

A baseline definition of "fever" is important in determining whether a patient's report of an elevated temperature warrants an FUO workup. Most temperatures are measured orally for both practical and physiologic purposes. A "normal" core (internal) body temperature ranges from 96º Fahrenheit (F) (35.6º Celsius [C]) to 100.8ºF (38.2ºC) in healthy persons, with a mean of 98.2ºF (36.8ºC). Core temperature in the afternoon is about 1ºF higher later in the day and may be a bit higher in women.

The temperature of the sublingual fossa correlates most closely, and changes most consistently, with core body temperature, which is fairly constant; the rectum and axilla do not, especially during sepsis. The tympanic membrane also correlates with core body temperature and is nearest to the hypothalamic center that regulates temperature, but accuracy depends on user technique and whether the ear canal is obstructed (eg, by wax); cold weather also cools the tympanic membrane. [6]

For the purposes of this article, the term FUO refers to the classic category, which focuses on the adult population. The definition of FUO in the pediatric age group varies, with a time frame ranging from 1-3 weeks in the literature. In this age group, the differential diagnoses are led by infections, followed by collagen vascular diseases; malignancy is typically not heralded by fever alone in children. [7] This article excludes FUO in the setting of impaired immunity such as HIV disease, solid-organ and bone marrow transplantation, and neutropenia. Disease-specific diagnostic algorithms in these conditions are described elsewhere. Regardless of age group, most clinicians define FUO as a persisting conundrum with few or no objective clues.
Causes of FUO may differ geographically based on regional exposures, economic development, and available diagnostic tools. For example, in developing countries, infection may predominate, while noninfectious inflammatory and malignant conditions are more common in developing countries. The focus of this article is FUO in developing countries; however, travel-associated causes that may present from developing countries should not be missed.

The list of etiologic possibilities is extensive, and it is helpful to break the differential diagnoses into broader categories, such as infection, noninfectious inflammatory conditions, malignancies, and miscellaneous. In recent years, noninfectious inflammatory disorders predominate, with infection now second.

A prospective review of FUO in 290 subjects between 1990 and 1999 found noninfectious inflammatory diseases in 35.2% of cases, infections in 29.7%, miscellaneous causes in 19.8%, and malignancies in 15.1%. Most were diagnosed within 3 visits or 3 hospital days. This differs from prior estimates, in which infections dominated, followed by malignancies, collagen vascular diseases, and numerous miscellaneous conditions. With the increasing use of immunomodulators used to treat an expanding range of conditions, infection may yet regain its lead as the cause of FUO. Interestingly, the rate of unknown causes is higher in this report than in prior estimates, with 33.8% remaining undiagnosed beyond 7 days. The short time frame may overestimate the number of undiagnosed cases. Evaluations in the past may not have proceeded as quickly, and, even now, newer tests may require transport to specialty laboratories, and diagnosis may still take longer than 7 days. [8]

The causes of FUO are often common conditions presenting atypically. Listed below are the most common, less common, and least common in their respective categories, but by no means the only causes.

Noninfectious Inflammatory Causes of FUO (Connective Tissue Diseases, Vasculitides, and Granulomatous Disorders)

The most common noninfectious inflammatory causes of FUO include the following:

- Giant cell (temporal) arteritis
- Adult Still disease (juvenile rheumatoid arthritis)

Less-common noninfectious inflammatory causes of FUO include the following:

- Systemic lupus erythematosus (SLE)
- Periarteritis nodosa/microscopic polyangiitis (PAN/MPA)
- Rheumatoid arthritis (RA)

The least common noninfectious inflammatory causes of FUO include the following:

- Antiphospholipid syndrome (APS)
- Gout
- Pseudogout
- Behçet disease
• Sarcoidosis
• Felty syndrome
• Takayasu arteritis
• Kikuchi disease
• Periodic fever adenitis pharyngitis aphthous ulcer (PFAPA) syndrome

Infectious Causes of FUO

The most common infectious causes of FUO include the following:

• Tuberculosis (TB)
• Q fever (parturient animals)
• Brucellosis (hooved mammals, raw dairy)

Less-common infectious causes of FUO include the following:

• HIV infection
• Abdominopelvic abscesses
• Cat scratch disease (CSD)
• Epstein-Barr virus (EBV) infection
• Cytomegalovirus (CMV) infection
• Enteric (typhoid) fever
• Toxoplasmosis
• Extrapulmonary TB

The least common infectious causes of FUO are listed below.

Organ-based infectious causes of FUO are as follows:

• Subacute bacterial endocarditis (SBE)
• Tooth abscess
• Chronic sinusitis/mastoiditis
• Chronic prostatitis
• Discitis
• Vascular graft infections
• Whipple disease
• Multicentric Castleman disease (MCD)
• Cholecystitis
- Lymphogranuloma venereum (LGV)

Geographic and travel-related considerations for FUO are listed below.

Tickborne infections, as follows:
- Babesiosis, Ehrlichiosis (southeast and central United States)
- Anaplasmosis (northeast and north central United States)
- Tickborne relapsing fever (rodent-infested cabins)

Regional infections, as follows:
- Histoplasmosis (Midwest United States, Ohio and Mississippi River Valleys, Central and South America, bat/bird droppings)
- Coccidiomycosis (southwest United States)
- Leptospirosis (tropics, freshwater swimming, triathlons, "mud run" races)
- Visceral leishmaniasis (Latin America, Middle East)
- Rat-bite fever (rat bite, food or water)

Malignant and Neoplastic Causes of FUO

Malignant and neoplastic causes of FUO are as follows:
- Most common: Lymphoma, renal cell carcinoma
- Less common: Myeloproliferative disorder, acute myelogenous leukemia
- Least common: Multiple myeloma, breast/liver/pancreatic/colon cancer, atrial myxoma, metastases to brain/liver, malignant histiocytosis

Miscellaneous Causes of FUO

Miscellaneous Causes of FUO are as follows:
- Most common: Cirrhosis (due to portal endotoxins), drug fever
- Less common: Thyroiditis, Crohn disease (regional enteritis)
- Least common: Pulmonary emboli, hypothalamic syndrome, familial periodic fever syndromes, cyclic neutropenia, factitious fever (especially in those experienced with the healthcare field)

**Prognosis**

Despite extensive differential diagnoses, patients with FUO that remains undiagnosed after an intensive and rational diagnostic evaluation generally have a reassuringly benign long-term course.