**Etiologies of fever of unknown origin in adults**

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**INTRODUCTION**

Clinicians commonly refer to a febrile illness without an initially obvious etiology or without localizing signs as fever of unknown origin (FUO). This usage is not accurate. Most febrile illnesses either resolve before a diagnosis can be made or develop distinguishing characteristics that lead to a diagnosis. FUO refers to a prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing.

Large case series of FUO applying this definition have been collected over a number of decades; these facilitate an approach to patients with FUO and an understanding of the changing patterns of FUO with time and newer diagnostic techniques.

The common and uncommon entities causing FUO in adults will be reviewed here. The definitions of this condition, an approach to the adult with FUO, and the etiology of FUO in children are discussed separately. (See ["Approach to the adult with fever of unknown origin"](https://www.uptodate.com/contents/approach-to-the-adult-with-fever-of-unknown-origin?search=fever&topicRef=2737&source=see_link) and ["Fever of unknown origin in children: Etiology"](https://www.uptodate.com/contents/fever-of-unknown-origin-in-children-etiology?search=fever&topicRef=2737&source=see_link).)

Three general categories of illness account for the majority of "classic" FUO cases and have been consistent through the decades:

●Infections

●Connective tissue diseases (eg, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica)

●Malignancies

**COMMON CAUSES**

The most prevalent causes of FUO are infection, noninfectious inflammatory diseases, and malignancy [[1-9](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/1-9)]. Infections and malignancies as causes of FUOs have decreased over time, while inflammatory diseases and undiagnosed fevers have increased ([table 1A-B](https://www.uptodate.com/contents/image?imageKey=ID%2F54701%7EID%2F66395&topicKey=ID%2F2737&search=fever&source=see_link) and [figure 1](https://www.uptodate.com/contents/image?imageKey=PC%2F73878&topicKey=ID%2F2737&search=fever&source=see_link)) [[10](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/10)].

Infections and noninfectious inflammatory diseases each account for 15 to 25 percent of FUOs, while malignancies cause less than 20 percent of these fevers. The rate of no diagnosis in studies published since 1990 has varied widely from 9 to 51 percent [[3-8,11](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/3-8,11)]. The prevalence of various febrile conditions also reflects geography, subpopulations under study, host and microbial factors, and hospital and health services.

In one of the latest published series, 73 patients from the Netherlands seen between December 2003 and July 2005 were evaluated for FUO [[8](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/8)]. The following distribution of causes was noted:

●Connective tissue diseases – 22 percent

●Infection – 16 percent

●Malignancy – 7 percent

●Miscellaneous – 4 percent

●No diagnosis – 51 percent

Most adults who remain undiagnosed after an extensive evaluation have a good prognosis [[11](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/11)]. (See ["Approach to the adult with fever of unknown origin", section on 'Outcome'](https://www.uptodate.com/contents/approach-to-the-adult-with-fever-of-unknown-origin?sectionName=OUTCOME&search=fever&topicRef=2737&anchor=H23&source=see_link#H23).)

**Infections** — Among infections, tuberculosis and abscesses are the most common etiologies.

**Tuberculosis** — Tuberculosis (TB) is the single most common infection in most FUO series. Presentations of TB, which escape early detection, are either extrapulmonary, miliary, or occur in the lungs of patients with significant preexisting pulmonary disease or immunodeficiency. As an example, pulmonary tuberculosis in patients with AIDS is often subtle, and the chest radiograph is normal in 15 to 30 percent of cases [[12,13](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/12,13)]. (See ["Diagnosis of pulmonary tuberculosis in adults"](https://www.uptodate.com/contents/diagnosis-of-pulmonary-tuberculosis-in-adults?search=fever&topicRef=2737&source=see_link).)

Disseminated (miliary) TB is readily treatable, while death can occur in patients who remain untreated. Thus, a vigorous search for this disorder should be pursued.

The purified protein derivative skin test is positive in fewer than 50 percent of patients with TB who present with an FUO, usually due to cutaneous anergy [[14](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/14)]. The interferon-gamma release assay also has low sensitivity for the diagnosis of active TB [[15](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/15)]. Sputum samples are positive in only one-quarter of cases. Because of these difficulties, establishing the diagnosis often requires biopsy of affected nodes, bone marrow, or liver.

Techniques for isolation of *Mycobacterium tuberculosis* from blood include isolator cultures and polymerase chain reaction (PCR) on BACTEC blood culture bottles with evidence of early growth [[16,17](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/16,17)]. Both of these methods have yielded positive results in approximately 16 days, although PCR may be more sensitive and specific [[17](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/17)].

**Abscess** — Occult abscesses are usually located in the abdomen or pelvis. Underlying conditions, which predispose to abscess formation, include cirrhosis, steroid or immunosuppressive medications, recent surgery, and diabetes. Abscesses arise when there has been disruption of a barrier such as the bowel wall in appendicitis, diverticulitis, or inflammatory bowel disease. The rupture often seals off spontaneously and local peritonitis is converted to an abscess by host defense mechanisms. Intraabdominal abscesses can develop in subphrenic, omental, pouch of Douglas, pelvic, and retroperitoneal locations in addition to visceral sites.

The source of infection in these abscesses can vary with the site of abscess formation:

●Pyogenic liver abscesses usually follow biliary tract disease or abdominal suppuration such as appendicitis or diverticulitis. Amebic liver abscesses cannot be distinguished on clinical grounds from pyogenic abscesses; amebic serology is positive in more than 95 percent of cases of extraintestinal disease.

●Hematogenous seeding rather than contiguous spread accounts for the majority of splenic abscesses, which are often missed prior to autopsy; endocarditis is the most common infection currently associated with splenic abscess.

●Perinephric or renal abscesses usually arise from existing infection in the urinary tract, although urine cultures may be negative or only intermittently positive. (See ["Renal and perinephric abscess"](https://www.uptodate.com/contents/renal-and-perinephric-abscess?search=fever&topicRef=2737&source=see_link).)

**Osteomyelitis** — Osteomyelitis should be considered as a cause of FUO since localized symptoms in some sites may not be prominent. Examples include vertebral osteomyelitis and osteomyelitis of the mandible. (See ["Osteomyelitis in adults: Clinical manifestations and diagnosis"](https://www.uptodate.com/contents/osteomyelitis-in-adults-clinical-manifestations-and-diagnosis?search=fever&topicRef=2737&source=see_link).)

**Bacterial endocarditis** — Cultures are negative in 2 to 5 percent of patients with infective endocarditis even when the utmost care is taken in obtaining the proper number and volume of blood cultures. The frequency of negative cultures is higher in patients who have already been treated with antimicrobials, such as intravenous drug users who frequently self-administer antibiotics [[18](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/18)].

Culture negativity is particularly likely with the following organisms, which are more difficult to isolate in culture:

●*Coxiella burnetii* (Q fever) and *Tropheryma whipplei* occasionally cause endocarditis but will not grow using cell free media. (See ["Q fever endocarditis"](https://www.uptodate.com/contents/q-fever-endocarditis?search=fever&topicRef=2737&source=see_link) and ["Whipple's disease"](https://www.uptodate.com/contents/whipples-disease?search=fever&topicRef=2737&source=see_link).)

●*Brucella*, *Mycoplasma*, *Chlamydia*, *Histoplasma*, *Legionella*, and *Bartonella*will not grow unless special media or microbiologic methods are employed.

●*Haemophilus* spp, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* (the so-called HACEK group) will not be detected unless blood cultures are incubated for 7 to 21 days.

The microbiology laboratory should be notified when endocarditis or other infections with such organisms are suspected, since most laboratories routinely discard blood cultures when there has been no growth after seven days of incubation. (See ["Clinical manifestations and evaluation of adults with suspected left-sided native valve endocarditis"](https://www.uptodate.com/contents/clinical-manifestations-and-evaluation-of-adults-with-suspected-left-sided-native-valve-endocarditis?search=fever&topicRef=2737&source=see_link).)

Non–culture-based diagnostic modalities can be used to increase the diagnostic yield when culture-negative endocarditis is suspected (eg, serologic assays or polymerase chain reaction). (See ["Culture-negative endocarditis: Epidemiology, microbiology, and diagnosis", section on 'Diagnosis'](https://www.uptodate.com/contents/culture-negative-endocarditis-epidemiology-microbiology-and-diagnosis?sectionName=DIAGNOSIS&search=fever&topicRef=2737&anchor=H8&source=see_link#H8).)

Peripheral manifestations are rarely detected in subacute endocarditis presenting as FUO. Endocarditis in intravenous drug users is often right sided and lacks murmurs, and self-administration of antimicrobials may obscure the detection of bacteremia.

Transesophageal echocardiography is positive in over 90 percent of cases of infective endocarditis presenting as FUO [[14](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/14)]. False-positive results may be due to anatomic abnormalities or noninfective vegetations; false-negative results occur with small vegetations or those that have already embolized. (See ["Clinical manifestations and evaluation of adults with suspected left-sided native valve endocarditis", section on 'Echocardiography'](https://www.uptodate.com/contents/clinical-manifestations-and-evaluation-of-adults-with-suspected-left-sided-native-valve-endocarditis?sectionName=Echocardiography&search=fever&topicRef=2737&anchor=H14&source=see_link#H14).)

Rarely, other endovascular infections (eg, mycotic aneurysms, septic thrombophlebitis) can be occult causes of fever. (See ["Overview of infected (mycotic) arterial aneurysm"](https://www.uptodate.com/contents/overview-of-infected-mycotic-arterial-aneurysm?search=fever&topicRef=2737&source=see_link) and ["Suppurative (septic) thrombophlebitis"](https://www.uptodate.com/contents/suppurative-septic-thrombophlebitis?search=fever&topicRef=2737&source=see_link).)

**Connective tissue diseases** — Adult Still's disease in young and middle-aged adults and giant cell arteritis (GCA) in older individuals are the most common rheumatologic disorders presenting as FUO. GCA accounts for approximately 15 percent of cases of FUO in older adults [[14](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/14)].

**Adult Still's disease** — Adult Still's disease is an inflammatory disorder characterized by quotidian (daily) fevers, arthritis, and an evanescent rash. Patients with adult Still's disease have features similar to children with systemic juvenile idiopathic arthritis. (See ["Clinical manifestations and diagnosis of adult Still's disease"](https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-adult-stills-disease?search=fever&topicRef=2737&source=see_link) and ["Systemic juvenile idiopathic arthritis: Clinical manifestations and diagnosis"](https://www.uptodate.com/contents/systemic-juvenile-idiopathic-arthritis-clinical-manifestations-and-diagnosis?search=fever&topicRef=2737&source=see_link).)

**Giant cell arteritis** — The diagnosis of GCA should be considered in a patient over the age of 50 who complains of headache, abrupt loss of vision, symptoms of polymyalgia rheumatica (which can occur without signs of vasculitis), unexplained fever or anemia, and a high erythrocyte sedimentation rate. The manifestations of GCA, however, can vary and may be transient. Jaw claudication, if present, is helpful in suspecting the diagnosis of GCA. Temporal artery biopsy is suggested in all cases of suspected GCA. (See ["Clinical manifestations of giant cell arteritis"](https://www.uptodate.com/contents/clinical-manifestations-of-giant-cell-arteritis?search=fever&topicRef=2737&source=see_link).)

**Other** — Other rheumatic disorders also may present as an FUO, including polyarteritis nodosa [[19](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/19)], Takayasu's arteritis (which is common in Japan), granulomatosis with polyangiitis, and mixed cryoglobulinemia. (See appropriate topic reviews.)

**Malignancy** — The most common malignancies to present with FUO are:

●Lymphoma, especially non-Hodgkin's

●Leukemia

●Renal cell carcinoma

●Hepatocellular carcinoma or other tumors metastatic to the liver

The most frequent occult malignancies to cause fever are of reticuloendothelial origin (eg, lymphoma and leukemia). Fever is most often evident in advanced lymphomas or in those with aggressive histologic patterns. Computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis and bone marrow biopsy usually identifies the sites of involvement.

Myelodysplastic syndromes occasionally present with fever and subtle evidence on blood smear of maturation arrest or dysplastic changes in one or several of the blood cell lines. Aleukemic leukemias are usually of the myeloid line. The diagnosis is made by bone marrow biopsy. Multiple myeloma has also been reported as a cause of FUO [[20](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/20)].

Renal cell carcinoma presents with fever in approximately 20 percent of cases. Microscopic hematuria and erythrocytosis may occur, but frequently there are no urine sediment abnormalities and the hematocrit is normal. Other adenocarcinomas also can cause fever, often but not invariably in the presence of hepatic metastases.

Atrial myxomas are uncommon but present with fever in approximately one-third of cases. Other findings include arthralgias, emboli, and hypergammaglobulinemia. The diagnosis is usually established by echocardiography. (See ["Cardiac tumors"](https://www.uptodate.com/contents/cardiac-tumors?search=fever&topicRef=2737&source=see_link).)

**Drugs** — One-third of hospitalized patients suffer from adverse drug reactions, including "drug fever." Drugs cause fever by stimulating an allergic or idiosyncratic reaction or by affecting thermoregulation. Eosinophilia and rash accompany drug fever in only 25 percent of cases; thus, the absence of these findings should not preclude a search for a possible offending drug [[21](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/21)]. The most common drugs that cause fever include:

●Antimicrobials (sulfonamides, penicillins, [nitrofurantoin](https://www.uptodate.com/contents/nitrofurantoin-drug-information?search=fever&topicRef=2737&source=see_link), [vancomycin](https://www.uptodate.com/contents/vancomycin-drug-information?search=fever&topicRef=2737&source=see_link), antimalarials)

●H1- and H2-blocking antihistamines

●Antiepileptic drugs (barbiturates and [phenytoin](https://www.uptodate.com/contents/phenytoin-drug-information?search=fever&topicRef=2737&source=see_link))

●Iodides

●Nonsteroidal antiinflammatory drugs (including salicylates)

●Antihypertensive drugs ([hydralazine](https://www.uptodate.com/contents/hydralazine-drug-information?search=fever&topicRef=2737&source=see_link), [methyldopa](https://www.uptodate.com/contents/methyldopa-drug-information?search=fever&topicRef=2737&source=see_link))

●Antiarrhythmic drugs ([quinidine](https://www.uptodate.com/contents/quinidine-drug-information?search=fever&topicRef=2737&source=see_link), [procainamide](https://www.uptodate.com/contents/procainamide-drug-information?search=fever&topicRef=2737&source=see_link))

●Antithyroid drugs

●Contaminants such as [quinine](https://www.uptodate.com/contents/quinine-drug-information?search=fever&topicRef=2737&source=see_link) that accompany injected cocaine or heroin

A number of drugs rarely cause fever, such as [digoxin](https://www.uptodate.com/contents/digoxin-drug-information?search=fever&topicRef=2737&source=see_link) and aminoglycosides.

Drug reactions occur in as many as 24 percent of patients with AIDS, but rash and nausea are more common at presentation than fever. In two series of patients with AIDS, isolated fever occurred in 1.7 and 0 percent of cases [[5,22](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/5,22)].

Drug fever may occur shortly after initiating a medication. However, it is not uncommon for several weeks or, in some cases, months to years to elapse prior to the start of fever.

The diagnosis of drug fever is made by a therapeutic trial of stopping the suspected drug (with occasional rechallenge). Most patients will defervesce within 72 hours after substituting drugs, although some may not recover for weeks. Clearance of offending drug derivatives may be delayed if the derivatives become bound or haptenated on long-lived host proteins. Drugs of the same class should not be reintroduced in a therapeutic trial.

**LESS COMMON CAUSES**

Many of the uncommon causes of FUO are listed in the table ([table 2](https://www.uptodate.com/contents/image?imageKey=ID%2F62509&topicKey=ID%2F2737&search=fever&source=see_link)).

**Factitious fever** — Factitious fever is usually a manifestation of an underlying psychiatric condition that predominantly affects women and healthcare professionals. Patients with factitious fever feign illness for some secondary gain. They may also display evidence of self-mutilation and may have had multiple hospitalizations, invasive diagnostic tests (eg, cardiac catheterization), and surgery. The response to psychiatric intervention has been discouraging. (See ["Factitious disorder imposed on self (Munchausen syndrome)"](https://www.uptodate.com/contents/factitious-disorder-imposed-on-self-munchausen-syndrome?search=fever&topicRef=2737&source=see_link).)

Fever elevations may be fabricated through manipulation of thermometers. Manipulated temperature elevations can be extreme, sometimes exceeding 41ºC, and the fever cycles may not be accompanied by the expected patient behavior and physical signs such as chills, covering with blankets, cool extremities, sweats, warm extremities, and tachycardia. Current widespread use of electronic thermometers diminishes the opportunity to manipulate or exchange thermometers.

Fever also can be induced by taking medications to which patients are allergic (eg, phenolphthalein) or by injecting foreign matter parenterally (eg, milk, urine, culture material, feces). The resulting illness may be associated with polymicrobial bacteremia, episodes of bacteremia caused by different pathogens, or recurrent soft tissue infections.

**Disordered heat homeostasis** — Disordered heat homeostasis occasionally follows hypothalamic dysfunction (eg, following a massive stroke or anoxic brain injury) or abnormal heat dissipation (from skin conditions such as ichthyosis). Excess heat production may also occur from illnesses such as hyperthyroidism.

**Dental abscess** — Apical dental abscesses are a rare cause of persistent fever that can be overlooked by the patient and physician. Among the 20 case reports in the literature, most individuals defervesced following removal of the decayed teeth, with or without antimicrobial therapy [[23](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/23)]. Other conditions linked to oral disease include brain abscesses, meningitis, mediastinal abscesses, and endocarditis; these are more common than dental FUO.

**Concurrent infections** — The common occurrence of multiple concurrent opportunistic infections in FUO patients with AIDS confounds diagnosticians, particularly when CD4 counts are very low. These may include cytomegalovirus, *Mycobacterium avium* complex, *Pneumocystis jirovecii*, endemic fungi (eg, *Histoplasma capsulatum*), and gastrointestinal protozoa (eg, *Cryptosporidium*, *Microsporidium*).

Other types of immunocompromised hosts may also present with FUO caused by more than one infection. (See ["Overview of infections following hematopoietic cell transplantation"](https://www.uptodate.com/contents/overview-of-infections-following-hematopoietic-cell-transplantation?search=fever&topicRef=2737&source=see_link) and ["Infection in the solid organ transplant recipient"](https://www.uptodate.com/contents/infection-in-the-solid-organ-transplant-recipient?search=fever&topicRef=2737&source=see_link).)

Tickborne illnesses are becoming more prevalent and more widely distributed in the United States. Organisms that cause babesiosis, Lyme disease, and anaplasmosis/ehrlichiosis, which have varying incubation periods and different susceptibilities to antimicrobial agents, may infect an individual concurrently or serially and present as FUOs or relapsing fever syndromes. Furthermore, emerging pathogens such as *Borrelia miyamotoi* may further confound diagnostic efforts.

**Other infections** — A number of more obscure infections that are associated with FUO and usually have a pulmonary component include Q fever, leptospirosis, psittacosis, tularemia, and melioidosis. Other less common infections that cause FUO but do not have pulmonary manifestations include secondary syphilis, disseminated gonococcemia, chronic meningococcemia, visceral leishmaniasis, Whipple's disease, and yersiniosis. (See appropriate topic reviews.)

**Alcoholic hepatitis** — The characteristic signs and symptoms of alcoholic hepatitis are fever, hepatomegaly, jaundice, and anorexia. Fever is typically modest (<38.3°C). There are several characteristic laboratory abnormalities in alcoholic hepatitis. The most typical is serum aminotransferase elevations to less than 500 international units/L with a disproportionate elevation of aspartate aminotransferase (serum glutamic oxaloacetic transaminase) compared with alanine aminotransferase (serum glutamic pyruvic transaminase); the ratio is usually greater than 2.0, a value that is rarely seen in other forms of liver disease [[24](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/24)]. (See ["Clinical manifestations and diagnosis of alcoholic fatty liver disease and alcoholic cirrhosis"](https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-alcoholic-fatty-liver-disease-and-alcoholic-cirrhosis?search=fever&topicRef=2737&source=see_link).)

**Other** — A number of other noninfectious disorders may present as an FUO:

●Venous thrombosis and thromboembolism, although more common presentations include dyspnea, pleuritic pain, cough, and hemoptysis. (See ["Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism"](https://www.uptodate.com/contents/clinical-presentation-evaluation-and-diagnosis-of-the-nonpregnant-adult-with-suspected-acute-pulmonary-embolism?search=fever&topicRef=2737&source=see_link).)

●Hematoma (eg, from trauma, rupture of an aortic aneurysm, or spontaneously in an anticoagulated patient) with subsequent inflammation. The hip, pelvis, and retroperitoneum can hide a substantial amount of blood.

●Hyperthyroidism and subacute thyroiditis occasionally cause FUO, although these conditions most frequently are diagnosed clinically.

●Other endocrine causes of fever include pheochromocytoma and adrenal insufficiency [[25](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/25)].

●Hereditary periodic fever syndromes, such as familial Mediterranean fever, tumor necrosis factor receptor-1–associated periodic syndrome (also called TRAPS), hyper-IgD syndrome, Muckle-Wells syndrome, and familial cold autoinflammatory syndrome [[26](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/26)]. (See ["Clinical manifestations and diagnosis of familial Mediterranean fever"](https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-familial-mediterranean-fever?search=fever&topicRef=2737&source=see_link) and ["New-onset urticaria"](https://www.uptodate.com/contents/new-onset-urticaria?search=fever&topicRef=2737&source=see_link).)

**SUMMARY**

●Three general categories of illness account for the majority of "classic" fever of unknown origin (FUO) cases and have been consistent through the decades ([table 1A-B](https://www.uptodate.com/contents/image?imageKey=ID%2F54701%7EID%2F66395&topicKey=ID%2F2737&search=fever&source=see_link)). These categories are infections, connective tissue diseases, and malignancy. (See ['Introduction'](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults?search=fever&topicRef=2736&source=see_link#H1) above.)

●Among infections, tuberculosis and abscesses are the most common etiologies presenting as FUO. (See ['Infections'](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults?search=fever&topicRef=2736&source=see_link#H3) above.)

●Systemic juvenile idiopathic arthritis (formerly called Still's disease) in younger patients and giant cell arteritis in older individuals are the most common rheumatologic disorders presenting as FUO. (See ['Connective tissue diseases'](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults?search=fever&topicRef=2736&source=see_link#H8) above.)

●The most common malignancies to present with FUO are lymphoma, especially non-Hodgkin's, leukemia, renal cell carcinoma, and hepatocellular carcinoma or other tumors metastatic to the liver. (See ['Malignancy'](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults?search=fever&topicRef=2736&source=see_link#H12) above.)

●Drug fever due to a variety of drugs is also a common cause of FUO. (See ['Drugs'](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults?search=fever&topicRef=2736&source=see_link#H13) above.)

●There are many less common causes of FUO ([table 2](https://www.uptodate.com/contents/image?imageKey=ID%2F62509&topicKey=ID%2F2737&search=fever&source=see_link)). (See ['Less common causes'](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults?search=fever&topicRef=2736&source=see_link#H14) above.)

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**REFERENCES**

1. [Alt HL, Barker MH. Fever of unknown origin. JAMA 1930; 94:1457.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/1)
2. [PETERSDORF RG, BEESON PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961; 40:1.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/2)
3. [de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997; 76:392.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/3)
4. [Vanderschueren S, Knockaert D, Adriaenssens T, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. Arch Intern Med 2003; 163:1033.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/4)
5. [Miller RF, Hingorami AD, Foley NM. Pyrexia of undetermined origin in patients with human immunodeficiency virus infection and AIDS. Int J STD AIDS 1996; 7:170.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/5)
6. [Knockaert DC, Vanneste LJ, Bobbaers HJ. Fever of unknown origin in elderly patients. J Am Geriatr Soc 1993; 41:1187.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/6)
7. [Zenone T. Fever of unknown origin in adults: evaluation of 144 cases in a non-university hospital. Scand J Infect Dis 2006; 38:632.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/7)
8. [Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine (Baltimore) 2007; 86:26.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/8)
9. [Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: a clinical approach. Am J Med 2015; 128:1138.e1.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/9)
10. [Horowitz HW. Fever of unknown origin or fever of too many origins? N Engl J Med 2013; 368:197.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/10)
11. [Knockaert DC, Dujardin KS, Bobbaers HJ. Long-term follow-up of patients with undiagnosed fever of unknown origin. Arch Intern Med 1996; 156:618.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/11)
12. [Foley NM, Miller RF. Tuberculosis and AIDS: is the white plague up and coming? J Infect 1993; 26:39.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/12)
13. [Greenberg SD, Frager D, Suster B, et al. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). Radiology 1994; 193:115.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/13)
14. [Arnow PM, Flaherty JP. Fever of unknown origin. Lancet 1997; 350:575.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/14)
15. [Metcalfe JZ, Everett CK, Steingart KR, et al. Interferon-γ release assays for active pulmonary tuberculosis diagnosis in adults in low- and middle-income countries: systematic review and meta-analysis. J Infect Dis 2011; 204 Suppl 4:S1120.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/15)
16. [Tholcken CA, Huang S, Woods GL. Evaluation of the ESP Culture System II for recovery of mycobacteria from blood specimens collected in isolator tubes. J Clin Microbiol 1997; 35:2681.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/16)
17. [Smith MB, Bergmann JS, Woods GL. Detection of Mycobacterium tuberculosis in BACTEC 12B broth cultures by the Roche Amplicor PCR assay. J Clin Microbiol 1997; 35:900.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/17)
18. [Molavi A. Endocarditis: recognition, management, and prophylaxis. Cardiovasc Clin 1993; 23:139.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/18)
19. [Kamimura T, Hatakeyama M, Torigoe K, et al. Muscular polyarteritis nodosa as a cause of fever of undetermined origin: a case report and review of the literature. Rheumatol Int 2005; 25:394.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/19)
20. [Mueller PS, Terrell CL, Gertz MA. Fever of unknown origin caused by multiple myeloma: a report of 9 cases. Arch Intern Med 2002; 162:1305.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/20)
21. [Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. Ann Intern Med 1987; 106:728.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/21)
22. [Harb GE, Alldredge BK, Coleman R, Jacobson MA. Pharmacoepidemiology of adverse drug reactions in hospitalized patients with human immunodeficiency virus disease. J Acquir Immune Defic Syndr 1993; 6:919.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/22)
23. [Siminoski K. Persistent fever due to occult dental infection: case report and review. Clin Infect Dis 1993; 16:550.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/23)
24. [Cohen JA, Kaplan MM. The SGOT/SGPT ratio--an indicator of alcoholic liver disease. Dig Dis Sci 1979; 24:835.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/24)
25. [Simon HB, Daniels GH. Hormonal hyperthermia: endocrinologic causes of fever. Am J Med 1979; 66:257.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/25)
26. [Drenth JP, van der Meer JW. Hereditary periodic fever. N Engl J Med 2001; 345:1748.](https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults/abstract/26)