Fever of unknown origin in adults: Etiologies

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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.

The most common causes of FUO in adults will be reviewed here. The evaluation and management of the adult with FUO, and the etiology of FUO in children, are discussed separately. (See "Fever of unknown origin in adults: Evaluation and management" and "Fever of unknown origin in children: Etiology".)

There are myriad causes of classic FUO, and determining an etiology is often difficult because fever is a nonspecific and common finding in many diseases. It has been estimated that over 200 causes of classic FUO have been documented in the literature [1,2].

This topic discusses etiologies of **classic** fever or unknown origin. Other categories of FUO, not discussed in this topic, include health care-associated FUO, FUO in immunocompromised patients, and travel-associated FUO. These categories are discussed elsewhere:

- (See "Fever of unknown origin in adults: Evaluation and management", section on 'Health care-associated FUO'.)

- (See "Fever of unknown origin in adults: Evaluation and management", section on 'FUO in immunocompromised patients'.)
- (See "Fever of unknown origin in adults: Evaluation and management", section on 'Travel-associated FUO'.)

DEFINITION OF CLASSIC FUO

Fevers of unknown origin are typically divided into one of four categories. This topic discusses "classic FUO," which is typically defined as a temperature >38.3˚C (100.9˚F) recorded on several occasions for >3 weeks despite appropriate initial inpatient or outpatient evaluation [3]. Some experts have more recently proposed that the temperature threshold be decreased from >38.3˚C to >38.0˚C (100.4˚F) (table 1) [3].

Definitions of categories of FUO other than classic FUO are found elsewhere. (See "Fever of unknown origin in adults: Evaluation and management", section on 'Definitions and categories of fuo'.)

OVERVIEW OF CAUSES

Observational data have led experts to classify causes of classic FUO into five different categories [1,2,4-16]. Meta-analyses have estimated the relative proportion of FUOs caused by diseases in each of these categories [2,4-6]:

- Infections (34 to 39 percent)
- Rheumatologic conditions (20 to 23 percent)
- Neoplasms (12 to 16 percent)
- Miscellaneous causes (6 to 7 percent)
- Undiagnosed (20 to 25 percent)

EPIDEMIOLOGY

The epidemiology of classic FUO is influenced by factors such as geographic location and patient age [2].

Changes over time — As medical care and socioeconomic conditions have changed, some studies have reported that the proportion of FUOs due to infection has steadily decreased (figure 1) [2,17,18].

However, comparing studies from different decades may lead to inaccurate conclusions due to advancements in medications (antimicrobials and nonantimicrobials), emergence of new diseases, and changes in diagnostic techniques and the practice of medicine over time [2,17,18].

Geographic variation — The causes of classic FUO vary by geographic location, particularly the proportion of FUOs caused by infection [2,4,5]. The top ten causes of FUO by region can be seen in the graphic (figure 2).

Factors that contribute to variation include geographic differences among endemic infections, such as tuberculosis and brucellosis, genetic predispositions to certain diseases, and the financial and medical resources in each locale [2].

Influence of patient-age — Data suggest that the breakdown of causes of FUO varies based on patients' ages.

Studies have reported that older adults (ie, >65 years old) are more likely than younger adults (<65 years old) to ultimately have an etiology identified, whereas no specific cause of fever is found in a higher proportion of younger adults [12,19,20]. Frequent diagnoses in older adults include giant-cell arteritis, urinary tract infection, and malignancy.

Effects of climate change — As the earth warms due to climate change, some experts anticipate changes in the distribution of infectious diseases, including those known to cause FUO [21]. Pathogens, vectors, and animal hosts propagate in certain climates, dependent upon temperature and humidity.

Extreme weather events may impact the environmental burden of pathogens; for example, areas affected by flood are at increased risk of waterborne pathogens and pathogens that thrive in unsanitary conditions (eg, enteric fever, leptospirosis), whereas areas affected by increased drought may more easily disperse endemic fungal pathogens (eg, *Coccidioidomycosis*) into the air.

Furthermore, climate-related human migration may drive susceptible people into areas with endemic disease and push those with infection into areas where disease is not present.

It is not uncommon for the epidemiology of infectious diseases to change over time. For example, there are proven instances of infectious organisms entering new locales via cross-country travel of humans, animals, or vectors (eg, COVID-19, carbapenem-resistant Enterobacterales) [22,23]. For scientists, proving that climate change is the primary cause of changing epidemiology of infectious diseases remains a challenge.

INFECTIONS

Infections are the most common worldwide cause of FUO, responsible for 34 to 39 percent of cases based on available data [2,4-6]. (See 'Overview of causes' above.)

The likelihood of an infectious etiology varies by geography. For instance, in Southeast Asia, approximately half of all FUOs are due to infections, whereas approximately 30 percent of FUOs in Europe are from infection [2,4,5].

Furthermore, infectious causes vary geographically. A map of the most common infectious causes of FUO by region can be seen in the graphic (figure 3).

Generalized infections — Generalized infections present diagnostic challenges because they have nonspecific presenting features.

Tuberculosis — In most case series, tuberculosis (TB) is among the top three causes of classic FUO [2,4-6]. Data suggest that TB is the top cause of FUO in Europe (responsible for 16 percent of cases), Southeast Asia (32 percent of cases), and the Western Pacific (18 percent of cases) (figure 3).

Extrapulmonary TB is more likely to cause FUO than pulmonary TB, which is usually evident on chest radiography. Extrapulmonary TB can manifest in different regions of the body, including lymph nodes, liver, bone marrow, pleura, pericardium, bone, joints, central nervous system, adrenal glands, genitourinary tract, and other systems. Typically, tissue biopsy or sampling of bodily fluid is necessary to make the diagnosis. (See "Tuberculous lymphadenitis" and "Bone and joint tuberculosis" and "Abdominal tuberculosis" and "Urogenital tuberculosis" and "Central nervous system tuberculosis: An overview".)

Miliary TB, another form of TB, is due to ongoing hematogenous spread of TB organisms and is characterized by numerous small bilateral lung nodules with, in some cases, simultaneous involvement of organs outside the lungs. Like extrapulmonary TB, diagnosis of miliary TB requires confirmation of the organism in tissue biopsy or bodily secretions. Acid-fast staining and positive cultures are less likely to be positive in patients with miliary TB, and multiple samples are often necessary to confirm the diagnosis. (See "Clinical manifestations, diagnosis, and treatment of miliary tuberculosis".)

Of note, the tuberculin skin test (TST) and interferon-gamma release assays (IGRA) lack sensitivity and specificity in patients with any form of active TB, especially miliary TB [24,25]. While a positive test increases the likelihood of active TB, it does not confirm the diagnosis;

likewise, a negative test does not rule out active TB. (See "Diagnosis of pulmonary tuberculosis in adults", section on 'All patients' and "Clinical manifestations, diagnosis, and treatment of miliary tuberculosis", section on 'Clinical approach'.)

Mononucleosis-like syndromes — Often, classic FUO is due to unusual presentations of common illnesses, such as common viral infections. Many patients with common viral infections will report close contact with sick individuals.

The most common causes are organisms that cause mononucleosis-like syndromes (ie, fever, pharyngitis, and lymphadenopathy):

- **Epstein-Barr virus (EBV)** – EBV is the classic cause of mononucleosis and typically infects teenagers and young adults, although it can infect older patients as well. In addition to fever, lymphadenopathy, and sore throat, it also commonly causes headache, persistent severe fatigue, and splenomegaly. Lymphadenopathy of the posterior cervical nodes is most common, although any nodes can be enlarged. Some patients present without pharyngitis and are described as having the "typhoidal form" of illness.

  Characteristic lab results primarily include lymphocytosis with atypical lymphocytes. Rapid diagnosis can be achieved by testing for heterophile antibodies (ie, the "Monospot" test), but this test can be negative in 10 to 30 percent of patients, particularly in those with the typhoidal form of illness. EBV infection in patients with negative heterophile antibody tests can be confirmed by testing for EBV-specific antibodies. (See "Infectious mononucleosis".)

- **Acute HIV syndrome** – Acute human immunodeficiency virus (HIV) infection can cause symptoms similar to those of EBV-associated mononucleosis. It is discussed further below. (See 'Acute HIV syndrome' below.)

- **Acute cytomegalovirus infection** – Patients with acute cytomegalovirus (CMV) often present with fever, headache, and malaise without pharyngitis or enlarged cervical lymph nodes. They are less likely to have splenomegaly, may not have atypical lymphocytes, and may be more likely to have elevated aminotransferases. (See "Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults", section on 'CMV mononucleosis'.)

  Diagnosis of acute CMV is hampered by suboptimal tests. Serologic tests lack specificity for acute illness, whereas antigen and molecular tests may detect viral shedding that is not necessarily indicative of symptomatic infection. (See "Overview of diagnostic tests for cytomegalovirus infection".)

- **Acute toxoplasmosis** – *Toxoplasma gondii* is a less common cause of mononucleosis-like illness than EBV, CMV, and HIV. It is a parasitic infection that causes symptoms and signs similar to other causes of mononucleosis; lymphadenopathy can persist for weeks. Mild atypical lymphocytosis may be present. Main risk factors are ingestion of undercooked meat in resource-abundant countries, exposure to contaminated water sources in resource-limited countries, and exposure to cat feces.

  The diagnosis of acute toxoplasmosis is made by serologic testing with immunoglobulin (Ig)M antibody tests and/or acute and convalescent IgG antibody tests. (See "Toxoplasmosis: Acute systemic disease".)

Acute HIV syndrome — In the early stages of HIV infection, patients may present with an unexplained febrile illness consistent with mononucleosis. Early recognition of HIV infection is important because it prevents further transmission and allows early treatment, which affords long-term benefit to the patient. Features suggestive of acute HIV include fever, lymphadenopathy, sore throat, myalgia, and headache. The presence of painful oral ulcers, rash, and relevant sexual exposures should increase suspicion of acute HIV (table 2). (See "Acute and early HIV infection: Clinical manifestations and diagnosis", section on 'Clinical features'.)

Patients may or may not report risk factors, such as recent sexual activity or injection drug use, but the diagnosis should be considered in all patients with mononucleosis-like illness because not all patients reveal their risk factors. In patients with compatible symptoms, diagnosis can be confirmed by a positive HIV viral load or antigen test coupled with a negative HIV antibody test. (See "Acute and early HIV infection: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

Brucellosis — Data suggest that brucellosis is the most common cause of FUO in the Eastern Mediterranean region and is the second most common cause in the Western Pacific region [4]. Brucellosis is endemic in the Mediterranean basin, the Middle East, Central Asia, China, the Indian subcontinent, sub-Saharan Africa, and parts of Mexico and Central and South America (table 3). (See "Brucellosis: Epidemiology, microbiology, clinical manifestations, and diagnosis".)

The primary risk factor for brucellosis is consumption of unpasteurized animal products, especially unpasteurized dairy products (eg, raw mild, soft cheese, butter). Clinical manifestations may include persistent fever and malaise, arthralgia/arthritis, back pain, epididymitis or orchitis, hepatosplenomegaly, elevation of liver enzymes, and hematologic

abnormalities. A presumptive diagnosis can be made via serologic tests, but cultures of tissue or bodily fluids is often necessary.

Infective endocarditis — Endocarditis should be considered in the differential diagnosis in most patients with FUO, especially since it can be usually diagnosed with blood cultures and because it is associated with a high mortality if undiagnosed. Specific risk factors increase the likelihood, including prior endocarditis, known valvular or congenital heart disease, the presence of a prosthetic heart valve, and injection drug use. FUO with a new or changed murmur suggests the infection, but other presentations, such as stroke or bilateral lung nodules, can occur from embolic events. (See "Clinical manifestations and evaluation of adults with suspected left-sided native valve endocarditis" and "Right-sided native valve infective endocarditis" and "Prosthetic valve endocarditis: Epidemiology, clinical manifestations, and diagnosis".)

Most, but not all patients, will have positive blood cultures and the diagnosis can usually be confirmed by echocardiograph. The most common cause of blood-culture negative endocarditis is prior antimicrobial therapy, although organisms associated with culture-negative endocarditis include *Coxiella burnetiid* (Q fever), *Tropheryma whipplei* (Whipple's disease), *Brucella*, *Mycoplasma*, *Chlamydia*, *Histoplasma*, *Legionella*, and *Bartonella* [26]. Additionally, *Haemophilus* spp, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* (the so-called HACEK group) historically caused culture-negative endocarditis, although microbiologic isolation of these organisms has substantially improved.

Enteric (typhoid and paratyphoid) fever — Enteric fever is most prevalent in impoverished, overcrowded areas with poor access to sanitation. The highest incidence occurs in south-central Asia, Southeast Asia, and southern Africa. The disease is spread by contaminated food or water or sharing space with an infected individual.

Patients with enteric fevers typically present with fever and chills and may have relative bradycardia (lack of expected increase in heart rate during fever), but this finding is neither highly specific nor sensitive. During the second week of illness, the illness typically progresses to include abdominal pain. As the disease further progresses, hepatosplenomegaly and a rash ("rose spots") may develop; in some patients, intestinal perforation can occur.

Leukopenia may be a distinguishing feature, and increased transaminases are common and a useful diagnostic clue. The diagnosis is confirmed by positive blood culture, but bacteremia is not always present. Constipation rather than diarrhea may occur in some phases of the infection. In endemic areas, empiric treatment is often provided because of risk of severe

sequalae from untreated disease. (See "Enteric (typhoid and paratyphoid) fever: Epidemiology, clinical manifestations, and diagnosis".)

Malaria — The most common presentation of malaria is unexplained fever with new anemia and thrombocytopenia. The diagnosis is confirmed by visualization of malaria parasites on thick and thin blood smears (often, multiple smears on separate days are required) or positive polymerase chain reaction of blood.

In most patients with malaria, the diagnosis is made before the patient meets the definition of classic FUO. However, the diagnosis should be considered in any individual who lives or has traveled to an endemic area. Furthermore, malaria may be emerging in previously low-risk locales; for instance, in 2023, the first locally acquired cases since 2003 were reported in the United States [27-30]. (See "Malaria: Clinical manifestations and diagnosis in nonpregnant adults and children".)

Disseminated fungal infections — Endemic fungal infections (eg, histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis) can present with FUO and other manifestations, such as lymphadenopathy, hepatosplenomegaly, and hematologic abnormalities. Additional organs can be affected, depending on the specific pathogen.

Primary risk factors are outdoor exposure, especially to soil (or in the case of blastomycosis, mud) in endemic regions. Histoplasmosis and blastomycosis are endemic in the Midwestern, south-central and southeastern states, particularly in areas surrounding the Mississippi and Ohio River basins of the United States; coccidioidomycosis is endemic in the southwestern United States and northern Mexico, and paracoccidioidomycosis is endemic in southern Central America and northern South America (figure 4). (See "Pathogenesis and clinical manifestations of disseminated histoplasmosis" and "Clinical manifestations and diagnosis of blastomycosis" and "Manifestations and treatment of nonmeningeal extrathoracic coccidioidomycosis" and "Clinical manifestations and diagnosis of acute/subacute paracoccidioidomycosis" and "Clinical manifestations and diagnosis of chronic paracoccidioidomycosis".)

Other generalized infections — Numerous other infections can cause generalized or multifocal febrile syndromes. Examples include Q fever, leptospirosis, arthropod-borne infections (eg, *Bartonella quintana*, scrub typhus), schistosomiasis, and others (table 4).

Localized infections — Localized infections that cause FUO are typically due to common bacteria that present in an atypical fashion.

Abscess — Internal abscess, especially intra-abdominal abscess, is an important cause of FUO in some case series. Although some patients may have localized symptoms of pain, other patients may report no symptoms other than fever.

In rare cases, abscesses may be present in large muscles such as the psoas and posterior thigh. These and other abscesses (such as perirectal abscesses) typically manifest as localized pain.

Abscesses are typically identified by radiographic imaging and confirmed by fluid sampling or drainage.

Urinary tract and prostate infections — While urinary tract infections (UTIs) often present with symptoms of dysuria or urinary frequency, fever occasionally may be the only presenting sign. Simple cystitis and pyelonephritis are typically diagnosed early in the course of illness, so patients don't meet the definition of classic FUO. However, renal abscess, hydronephrosis complicated by infection, or prostatitis may present with fever alone. (See "Renal and perinephric abscess".)

The diagnosis of prostatitis can be especially elusive because fever and mild pelvic pain may be the only symptoms, and imaging and urine culture may be normal. Prostatitis is usually caused by enteric or sexually transmitted bacteria, although other causes include tuberculosis, blastomycosis, coccidioidomycosis, and meliodosis. (See "Chronic bacterial prostatitis".)

Sexually transmitted infections — Certain sexually transmitted infections can cause FUO with otherwise subtle symptoms. For example, acute HIV syndrome causes a mononucleosis syndrome (as described above); disseminated gonococcus can cause fever with arthralgia/arthritis and pustular skin rash; and pelvic inflammatory disease can cause fever with pelvic pain or dyspareunia. (See 'Acute HIV syndrome' above and "Disseminated gonococcal infection" and "Pelvic inflammatory disease: Clinical manifestations and diagnosis".)

Bone or joint infection — Bone and joint infections usually cause localized pain, but symptoms can be vague in certain individuals (eg, diabetic patients with neuropathy). In some cases, bone or joint infection is a sequela of disseminated infection; for example, tuberculosis, Lyme disease, endemic mycoses, gonococcal infection, and brucella may cause bone or joint infection due to systemic infection. Some atypical organisms also have a predilection for the spine, including tuberculosis, brucella, and blastomycosis.

Diagnosis of osteomyelitis is suggested on imaging and confirmed by bone biopsy. Joint infection is confirmed by synovial fluid cell count and culture. (See "Nonvertebral osteomyelitis in adults: Clinical manifestations and diagnosis" and "Vertebral osteomyelitis and discitis in adults" and "Septic arthritis in adults".)

Other localized infections — Other local infections that can cause FUO include chronic meningitis (infectious and noninfectious), dental infection, sinusitis, intra-abdominal infection (eg, cholecystitis, appendicitis, diverticulosis, liver abscess), and viral hepatitis [31].

RHEUMATOLOGIC DISEASES

Data suggest that rheumatologic conditions are responsible for approximately 20 percent of worldwide cases of FUO [4]. (See 'Overview of causes' above.)

Adult-onset Still's disease — Adult-onset Still's disease (AOSD) is the most common rheumatologic cause of classic FUO in many case series [2,4-6].

AOSD typically occurs between the ages of 15 and 45. The major clinical features are fever, rash, and arthritis or arthralgia. The classic rash in patients with AOSD is an evanescent, salmon-colored, macular or maculopapular rash on the trunk and extremities that occurs with fever and disappears during afebrile periods. Arthritis most often involves knees, wrists, ankles, and elbows. Sore throat is a common feature, and additional symptoms may include symmetrical cervical lymphadenopathy and splenomegaly.

The diagnosis of AOSD is based on clinical findings, compatible laboratory findings, and lack of evidence of other etiologies, such as systemic lupus erythematosus. Suggestive laboratory findings include marked elevation of ferritin (often above 3000 ng/mL), elevated erythocyte sedimentation rate (ESR) and C-reactive protein (CRP), and a neutrophilic leukocytosis. Anemia and thrombocytosis are also common. (See "Clinical manifestations and diagnosis of adult-onset Still's disease".)

Vasculitis — Any form of vasculitis can cause fevers.

Giant-cell arteritis — In older adults, especially those over 65 years old, giant-cell arteritis is one of the most common rheumatologic causes of classic FUO. Clinical features include headache, jaw claudication, and/or temporal artery tenderness. Transient monocular vision loss (amaurosis fugax) can be a harbinger of permanent vision loss; stroke is another potentially devastating complication.

Typical lab results include markedly elevated ESR and CRP. The diagnosis is confirmed by temporal artery biopsy. Empiric treatment with corticosteroids should be provided as soon as the diagnosis is considered to prevent possible blindness or stroke. (See "Clinical manifestations of giant cell arteritis" and "Diagnosis of giant cell arteritis" and "Treatment of giant cell arteritis".)

Patients with giant-cell arteritis may also have polymyalgia rheumatica, which manifests as pain and stiffness in the proximal muscles (eg, shoulder, thighs), especially in the mornings upon awakening. (See "Clinical manifestations and diagnosis of polymyalgia rheumatica".)

Other vasculitic syndromes — Other vasculitides reported to cause FUO include the following:

- **ANCA-associated vasculitis** – Vasculitic syndromes associated with antinuclear-cytoplasmic antibodies (ANCA) include granulomatosis with polyangiitis, microscopic polyangiitis, drug-induced ANCA-associated vasculitis, and others. Each ANCA-associated syndrome can affect multiple organ systems. For example, granulomatosis with polyangiitis (previously known as Wegener's granulomatosis) is associated with fever, malaise, arthralgia, nasal or sinus symptoms, pulmonary symptoms such as cough, and hematuria or other renal manifestations. (See "Clinical spectrum of antineutrophil cytoplasmic autoantibodies" and "Granulomatosis with polyangiitis and microscopic polyangiitis: Clinical manifestations and diagnosis".)

- **Polyarteritis nodosa** – The most common findings of polyarteritis nodosa (PAN) are rash (eg, purpura, livedo reticularis), hematuria or other renal manifestations, and mononeuritis multiplex (numbness and weakness in a single nerve). Other affected systems may include the gastrointestinal tract, genitourinary tract (eg, orchitis), and muscles. The diagnosis is confirmed by biopsy; no specific laboratory tests are diagnostic, although Hepatitis B infection is often associated with PAN. (See "Clinical manifestations and diagnosis of polyarteritis nodosa in adults".)

- **Behçet disease** – Behçet disease is most common in males 20 to 40 years of age in eastern Asia and the Mediterranean basin. Like other forms of vasculitis, multiple organs can be involved. The most common features of Behçet are oral and genital ulcers, various forms of rashes, ocular abnormalities (especially uveitis), arthritis, and venous thrombosis. (See "Clinical manifestations and diagnosis of Behçet syndrome".)

Systemic lupus erythematosus — Systemic lupus erythematosus (SLE) consistently ranks in the top three rheumatologic causes of classic FUO [2,4,5].

The diagnosis of SLE is based on clinical criteria and associated laboratory results. Patients typically present with fatigue, oral ulcers, polyarticular arthritis, and rash (malar rash is the most common). Other symptoms include pleuritis and/or pericarditis, renal disease, seizure or psychosis, and other findings. Laboratory results include positive antinuclear antibody (ANA) and other more specific autoantibodies. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults".)

Other rheumatologic conditions — Many other rheumatologic conditions can cause prolonged fevers. Examples include rheumatoid arthritis, mixed connective tissue disease, polymyositis, dermatomyositis, Sjogren's syndrome, systemic sclerosis, and IgA vasculitis (ie, Henoch-Schonlein purpura).

In addition, patients with rheumatoid arthritis can also have Felty syndrome, a complication of rheumatoid arthritis that manifests as neutropenia and splenomegaly; in such patients, fever in the setting of neutropenia should be treated with antibiotic therapy, as discussed elsewhere. (See "Clinical manifestations and diagnosis of Felty syndrome".)

MALIGNANCIES

In case series, malignancies represent 12 to 16 percent of causes of FUO worldwide [2,4-6]. (See 'Overview of causes' above.)

Lymphoma and other hematologic malignancies — Hematologic malignancies are the most common oncologic cause of classic FUO. In a meta-analysis of 19 prospective observational studies of patients with FUO, 89 percent of oncologic FUOs were due to hematologic malignancies.

- **Lymphoma** – Lymphoma is responsible for over half of all oncologic FUOs [2,4-6]. Most lymphomas will manifest as either palpable peripheral lymphadenopathy or pathologic lymphadenopathy on radiographic imaging. Splenomegaly may be present, and laboratory results often reveal hematologic abnormalities and elevated ESR and CRP. Patients with Hodgkin's lymphoma may describe a particular fever pattern known as a "Pel-Ebstein fever," characterized by fevers that gradually increase then return to normal over one to two weeks and then recur about one week later.

  Diagnosis of lymphoma is confirmed by biopsy. (See "Clinical presentation and initial evaluation of non-Hodgkin lymphoma" and "Clinical presentation and diagnosis of classic Hodgkin lymphoma in adults".)

- **Leukemia** – Leukemia should be suspected when abnormal white blood cells (WBCs) or WBC precursors are noted on peripheral smear or when marked elevations and/or severe thrombocytopena are present in the WBC. The diagnosis is confirmed by bone marrow biopsy. (See "Acute myeloid leukemia in adults: Overview" and "Clinical manifestations and diagnosis of chronic myeloid leukemia" and "Clinical manifestations, pathologic features, and diagnosis of B cell acute lymphoblastic leukemia/lymphoma".)

- **Myelodysplastic syndromes** – 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. (See "Clinical manifestations, diagnosis, and classification of myelodysplastic syndromes (MDS)".)

- **Multiple myeloma** – Multiple myeloma is due to neoplastic proliferation of plasma cells that produce a monoclonal immunoglobulin [32]. Clinical features include bone pain with lytic lesions on routine skeletal films, increased total serum protein and/or presence of monoclonal protein in urine or serum, unexplained anemia, hypercalcemia, and acute kidney failure with a bland urinalysis. The diagnosis is confirmed by bone marrow biopsy. (See "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis".)

Solid tumors — Fever is not a common presenting symptom in most types of solid-organ malignancy but has been reported, especially in patients with renal cell carcinoma. Up to 20 percent of patients with renal cell carcinoma present with fever [33]. Other malignant causes of FUO include colon cancer, hepatocellular carcinoma, glioblastoma multiforme, ovarian cancer, pancreatic cancer, and lung cancer [34]. Metastatic disease has also been reported to cause FUO.

Solid tumors are often suspected based on focal symptoms and/or radiographic imaging. The diagnosis is confirmed by biopsy. (See "Clinical manifestations, evaluation, and staging of renal cell carcinoma".)

MISCELLANEOUS CAUSES

Observational data suggest that 6 to 7 percent of classic FUOs are caused by diseases that are not infectious, rheumatologic, or oncologic in origin [2,4-6]. (See 'Overview of causes' above.)

Sarcoidosis — Sarcoidosis is a multisystem granulomatous disorder that most commonly presents with bilateral hilar adenopathy. Other manifestations may include pulmonary reticular or nodular opacities, various types of rashes, arthritis, ophthalmologic findings, hepatomegaly, and hypercalcemia. A minority of patients present with Lofgren syndrome, a syndrome characterized by fever, hilar adenopathy, and erythema nodosum or bilateral ankle arthritis.

The diagnosis of sarcoidosis requires biopsy and negative tests for other causes of similar disease (eg, tuberculosis, disseminated fungal infection, malignancy). (See "Clinical manifestations and diagnosis of sarcoidosis".)

Hemophagocytic lymphohistiocytosis — This syndrome is most common in children and young adults and is characterized by fever, splenomegaly, anemia, thrombocytopenia, markedly elevated serum ferritin, and hypertriglyceridemia or hypofibrinogenemia. The diagnosis is based on clinical criteria plus bone marrow or other tissue showing hemophagocytosis. Additional laboratory findings include specific immunologic studies. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis".)

Factitious fever — Factitious fever is usually a manifestation of an underlying psychiatric condition that predominantly affects women and health care professionals. Patients with factitious fever feign illness for some secondary gain. Patients with factitious fevers may also display evidence of self-mutilation and typically have a history of multiple hospitalizations, numerous negative diagnostic tests (eg, cardiac catheterization), and surgery. The response to psychiatric intervention has been discouraging. (See "Factitious disorder imposed on self (Munchausen syndrome)".)

Fever elevations may be fabricated through manipulation of thermometers. Manipulated temperature elevations can be extreme, sometimes exceeding 41°C, and 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.

Clues to factitious fever include lack of other objective signs of illness or witnesses to confirm the febrile episodes.

Drug fever — Drugs can cause fever by stimulating an allergic or idiosyncratic reaction or by affecting thermoregulation. Eosinophilia and/or rash are present in a minority of patients with drug fever; thus, the absence of these findings should not preclude a search for a possible offending drug [35,36]. Drug fever is discussed in detail elsewhere. (See "Drug fever".)

Familial mediterranean fever — This genetic disorder is most prevalent in individuals of Turkish, Armenian, Middle Eastern, and North African Jewish descent. Typical patients have recurrent attacks of fever along with serositis (eg, peritonitis, pleuritis, pericarditis, arthritis) or erysipelas-like erythema. The intervals between febrile episodes are irregular, ranging from one week to several months to years. The illness typically presents in adolescents and young adults

but can present at any age. The diagnosis is based on established clinical criteria. (See "Clinical manifestations and diagnosis of familial Mediterranean fever".)

Other miscellaneous conditions — Numerous other diseases can cause classic FUO. For example, disordered heat homeostasis due to hypothalamic dysfunction (eg, following a massive stroke or anoxic brain injury) may cause prolonged high fevers without other associated symptoms. (See "Pathophysiology and treatment of fever in adults", section on 'Fever, hyperpyrexia, and hyperthermia'.)

UNDIAGNOSED CAUSES

A diagnosis cannot be established in some patients with classic FUO despite careful evaluation and testing [2,4-6]. The prognosis of such patients may be good, as discussed separately. (See "Fever of unknown origin in adults: Evaluation and management", section on 'Outcomes'.)

SUMMARY AND RECOMMENDATIONS

- **Etiology by category** – Classic fevers of unknown origin (FUOs) are typically categorized into one of five general categories based on the underlying cause: infections, rheumatologic conditions, malignancies, miscellaneous causes, and undiagnosed causes. (See 'Overview of causes' above.)
- **Infections** – Infectious causes of FUO are highly dependent on the patient's geographic location and exposures (figure 3). (See 'Infections' above.)
  - **Generalized infections** – Worldwide, tuberculosis, brucellosis, and infective endocarditis are among the most common generalized infections presenting as FUO. (See 'Generalized infections' above.)
  - **Localized infections** – Abscess is the most frequently reported localized infection presenting as FUO. (See 'Localized infections' above.)
- **Rheumatologic conditions** – Adult-onset Still's disease in younger patients and giant-cell arteritis in older individuals are the most common rheumatologic disorders presenting as FUO (figure 2). (See 'Rheumatologic diseases' above.)
- **Malignancies** – Among the most common malignancies to present with FUO are lymphoma, leukemia, and renal cell carcinoma (figure 2). (See 'Malignancies' above.)

- **Miscellaneous causes** – There are many other causes of FUO, including sarcoidosis, hemophagocytic lymphohistiocytosis, factitious fever, and drug fever. (See 'Miscellaneous causes' above and "Drug fever".)

- **Undiagnosed cases** – An etiology cannot be identified in some patients with classic FUO despite undergoing a thorough evaluation. The prognosis of such patients may be good and many fevers self-resolve. (See 'Undiagnosed causes' above.)

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Topic 2737 Version 36.0

GRAPHICS

Category-based definitions of FUO

Category	Commonly used definition
Classic FUO	Temperature >38.3°C (100.9°F) recorded on several occasions for >3 weeks, despite 3 outpatient clinic evaluations, 1 week of intensive outpatient investigation, or 3 days of hospital-based evaluation.*
Health care-associated FUO	
▪ ICU patient	Temperature >38.3°C (100.9°F) recorded on several occasions in an ICU patient despite ≥3 days of investigations. Fever must not have been present or incubating on admission.
▪ Non-ICU patient	Same definition as for ICU patient, except patient is hospitalized but not critically ill.
▪ Post-operative patient	Same definition as for ICU patient, except fever is usually defined as ≥38.0°C (100.4°F).
FUO in immunocompromised patients¶	
▪ Neutropenic patients	Temperature ≥38.3°C (100.9°F) or ≥38.0°C (100.4°F) sustained over a one hour period, recorded on several occasions over at least 3 days, despite appropriate antimicrobial therapy. Neutropenia is defined as <500 neutrophils/microL or impending fall to that level within 48 hours.
▪ Patients with HIV and CD4 count <200 cells/microL	Temperature ≥38.3°C (100.9°F) recorded on several occasions for >3 weeks for outpatient or >3 days for inpatient despite appropriate evaluation.
Travel-associated FUO	Temperature >38.3°C (100.9°F) recorded on several occasions for >3 weeks, despite 3 outpatient clinic evaluations, 1 week of intensive outpatient investigation, or 3 days of hospital-based evaluation, in a patient who travelled to another country, typically within the prior 12 months.

FUO definitions vary. An overarching definition of FUO is fever in the absence of an identifiable cause despite reasonable evaluation in either the inpatient or outpatient setting; the fever must persist longer than typical or suspected self-limiting conditions, such as common viral illnesses. A specific temperature threshold to define a fever is debatable as well; most studies define fever as a temperature >38.3°C (100.9°F), although definitions range from 38.0°C (100.4°F) to 38.5°C (101.3°F).

FUO: fever of unknown origin.

* Because peak normal temperature in well individuals is 38.0°C, some experts have proposed a cut-off temperature for classic FUO of >38.0°C (100.4°F) instead of >38.3°C (100.9°F).[1]

¶ Formal definitions for FUO have not been defined for immunocompromising conditions other than neutropenia and HIV.

Reference:

1. *Wright WF, Mulders-Manders CM, Auwaerter PG, et al. Fever of unknown origin (FUO) – A call for new research standards and updated clinical management. Am J Med 2022; 135:173.*

Adapted from:

1. *Wright W, Mackowiak P. Fever of unknown origin. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed, Bennett J, Dolin R, Blaser M (Eds), Elsevier Saunders 2015. p. 721.*
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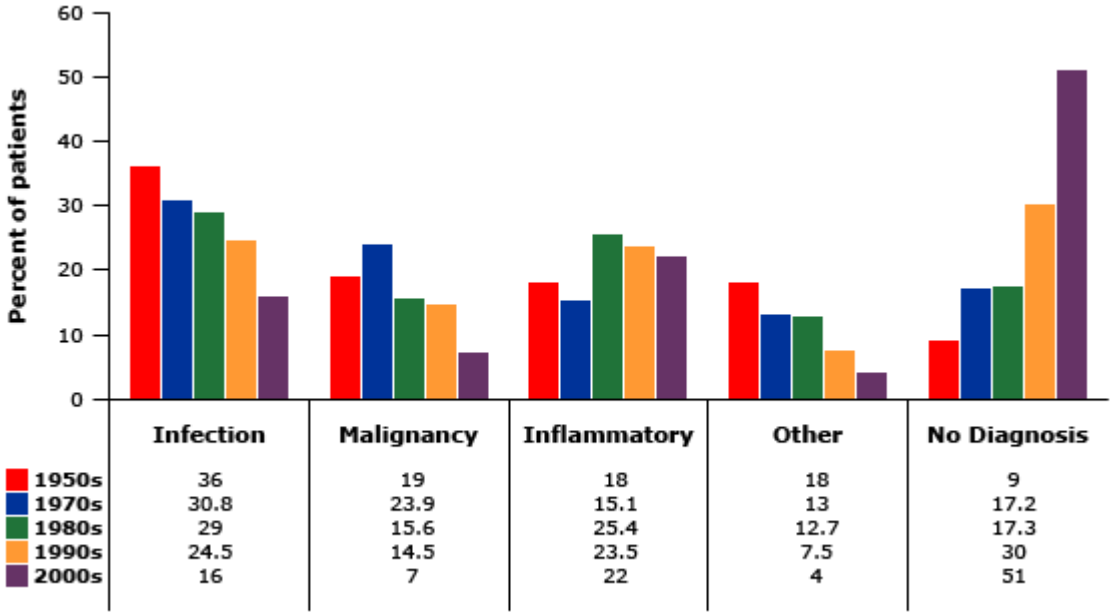
Graphic 143892 Version 1.0

The percentage of patients with fever of unknown origin by cause during four decades

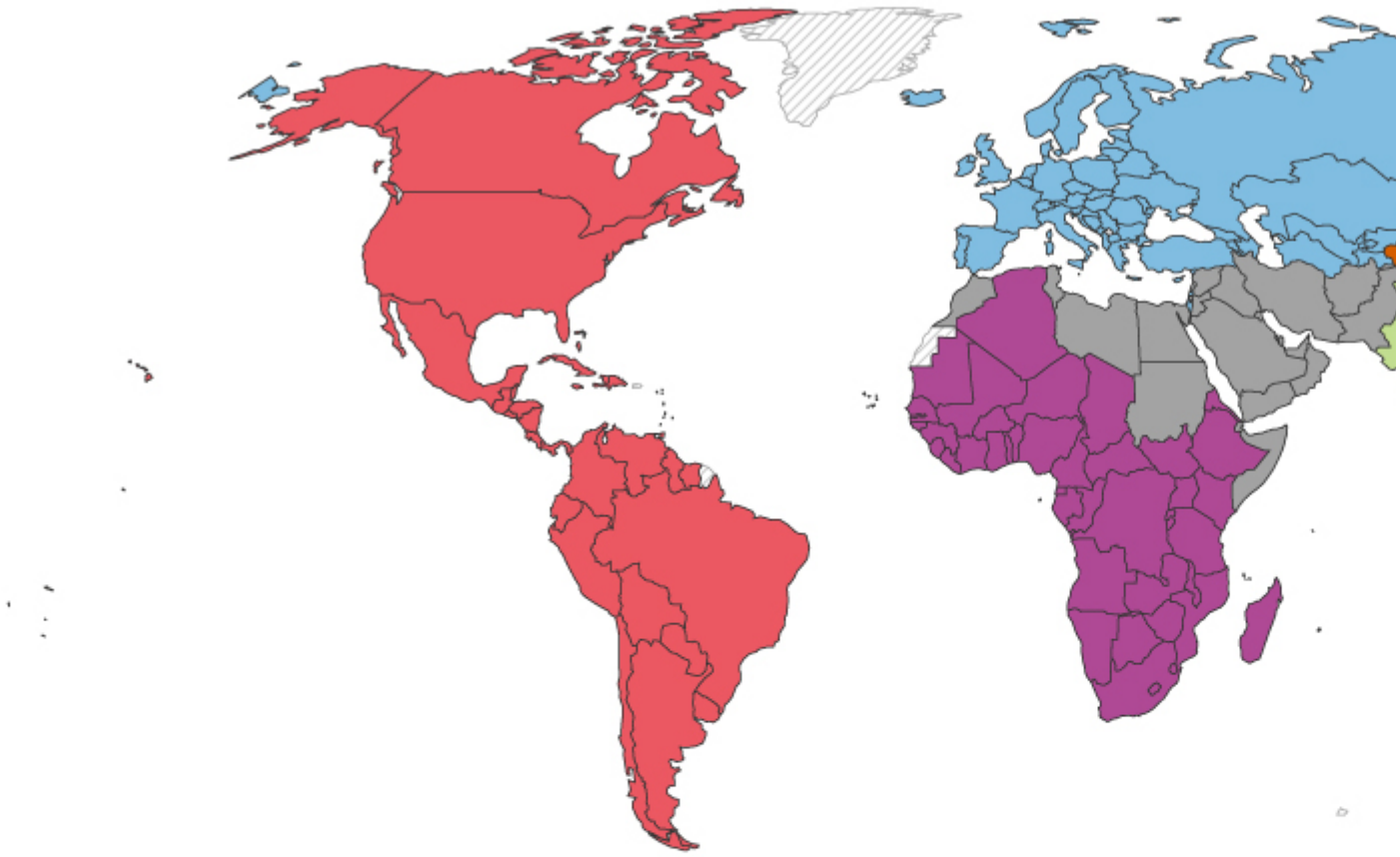


	Infection	Malignancy	Inflammatory	Other	No Diagnosis
1950s	36	19	18	18	9
1970s	30.8	23.9	15.1	13	17.2
1980s	29	15.6	25.4	12.7	17.3
1990s	24.5	14.5	23.5	7.5	30
2000s	16	7	22	4	51

Adapted from: Mourad O, Palda V, Detsky AS. Arch Intern Med 2003; 163:545.

Graphic 73878 Version 3.0

Top 10 causes of classic FUO by region



Africa

Limited data available

Americas

Limited data available

Eastern Mediterranean

1. Brucellosis, 13%
2. SLE, 11%
3. Viral infection, 11%
4. Tuberculosis, 9%
5. Endocarditis, 9%
6. UTI, 7%
7. Abscess, 6%
8. Enteric (typhoid and paratyphoid) fever, 5%
9. Non-Hodgkin's lymphoma, 4%
10. HIV, 4%

Europe

1. Tuberculosis, 16%
2. AOSD, 10%
3. Giant-cell arteritis, 6%
4. Endocarditis, 5%
5. UTI, 5%
6. Non-Hodgkin's lymphoma, 4%
7. Abscess, 4%
8. Viral infection, 4%
9. Brucellosis, 3%
10. Pneumonia, 3%

South-E

1. Tuber
2. Leuke
3. Enteri paraty
4. Non-H lymph
5. AOSD
6. Hodgk lymph
7. Endoc
8. HIV, 3
9. UTI, 3
10. Mala

The depicted regions are defined by the World Health Organization.

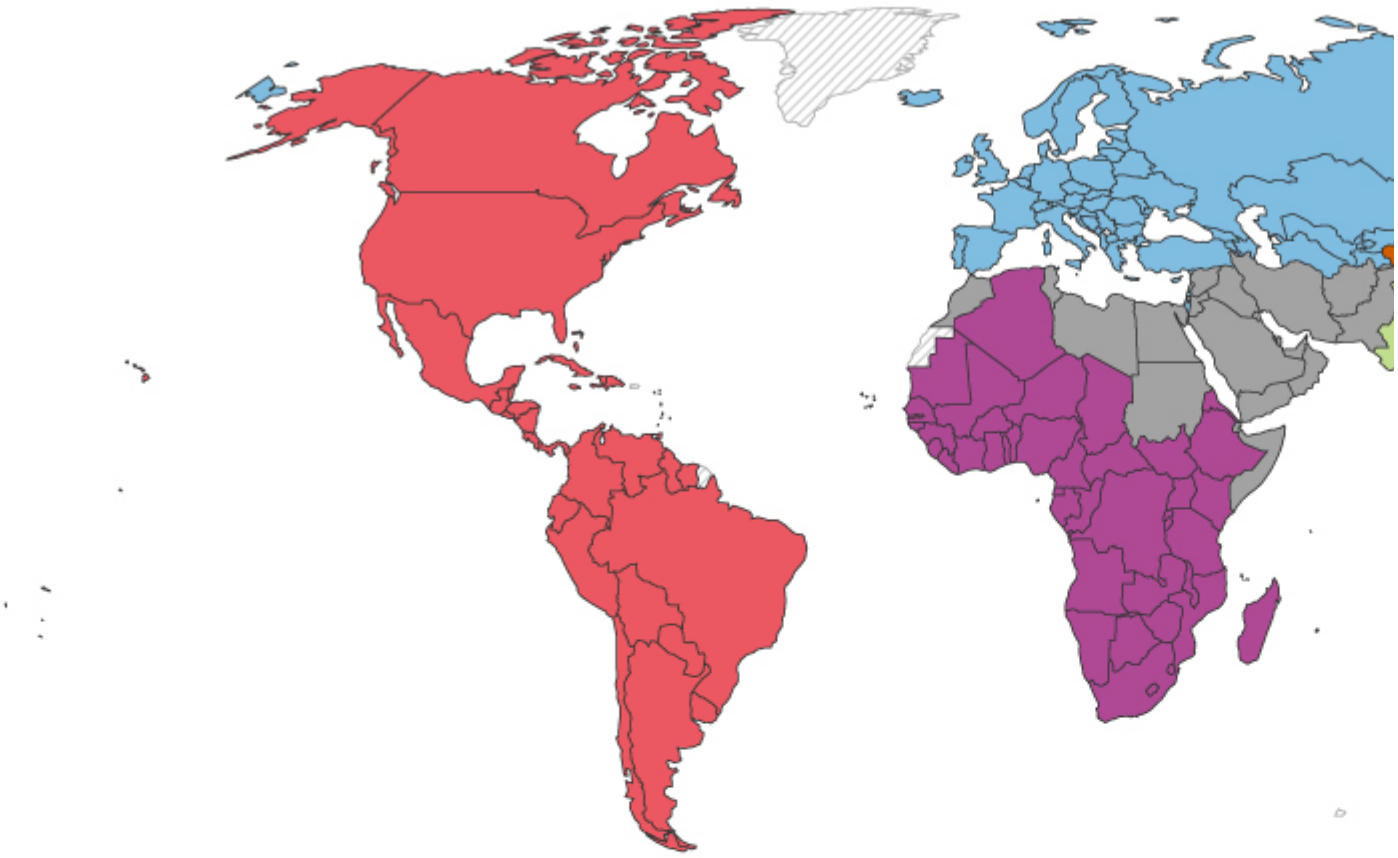
AOSD: Adult-onset Still's disease; FUO: fever of unknown origin; HIV: human immunodeficiency virus; SLE: systemic lupus erythematosus; UTI: urinary tract infection.

Data from: Wright WF, Yenokyan G, Auwaerter PG. Geographic influence upon noninfectious diseases accounting for fever of unknown origin: A systematic review and meta-analysis. Open Forum Infect Dis 2022; 9:ofac396.

Underlying map design from: Beltekian D. World map region definitions. Published online at OurWorldInData.org. © Global Change Data Lab. Available at: https://ourworldindata.org/world-region-map-definitions (Accessed November 20, 2023). Reproduced under the terms of the Creative Commons Attribution License 4.0.

Graphic 143465 Version 1.0

Infectious causes of classic FUO by region



Africa

Limited data available

Americas

Limited data available

Eastern Mediterranean

Proportion of FUO caused by infection: 37%

1. Brucellosis, 19%
2. Viral infection, 16%
3. Endocarditis, 14%
4. Tuberculosis, 14%
5. UTI, 11%
6. Abscess, 9%
7. Enteric (typhoid and paratyphoid) fever, 7%
8. HIV, 5%
9. Malaria, 2%
10. Pneumonia, 2%
11. STI, 2%

Europe

Proportion of FUO caused by infection: 30%

1. Tuberculosis, 31%
2. Endocarditis, 10%
3. UTI, 9%
4. Abscess, 7%
5. Viral infection, 7%
6. Brucellosis, 6%
7. Pneumonia, 6%
8. Enteric fever, 4%
9. Parasite, not malaria, 3%
10. Intraabdominal, non-abscess, 2%
11. Malaria, 2%
12. Yersiniosis, 2%
13. Other, 11%

South-East As

Proportion of F by infection: 4

1. Tuberculosis
2. Abscess, 8%
3. Enteric (typl paratyphoid)
4. HIV, 5%
5. Endocarditis
6. Malaria, 4%
7. Brucellosis,
8. UTI, 4%
9. Visceral leish
10. Viral infecti
11. Meningitis,
12. Pneumonia
13. Visceral lar
14. Other, 4%

The depicted regions are defined by the World Health Organization.

FUO: fever of unknown origin; HIV: human immunodeficiency virus; STI: sexually transmitted infection; UTI: urinary tract infection.

Data from: Wright WF, Yenokyan G, Auwaerter PG. Geographic influence upon noninfectious diseases accounting for fever of unknown origin: A systematic review and meta-analysis. Open Forum Infect Dis 2022; 9:ofac396.

Graphic 143466 Version 1.0

Clinical manifestations of acute HIV infection

Features (percent)	Overall (n = 378)	Male (n = 355)	Female (n = 23)	Sexual* (n = 324)	IVDU¶ (n = 34)
Fever	75	74	83	77	50
Fatigue	68	67	78	71	50
Myalgia	49	50	26	52	29
Skin rash	48	48	48	51	21
Headache	45	45	44	47	30
Pharyngitis	40	40	48	43	18
Cervical adenopathy	39	39	39	41	27
Arthralgia	30	30	26	28	26
Night sweats	28	28	22	30	27
Diarrhea	27	27	21	28	23

This table lists the most frequent clinical findings reported among patients with acute HIV infection from five prospective cohorts.

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* Homosexual or heterosexual route of transmission.

¶ IVDU, intravenous drug use as route of transmission.

Graphic 87682 Version 3.0

Brucellosis incidence by country (cases per 100,000 person-years)

Country	Study level	Incidence per 100,000 per year
North Africa and Middle East		
Egypt	Sub-national	0.28 to 70.00
Gaza	Sub-national	8.00
Iraq	Sub-national	52.29 to 268.81
Iran	Sub-national*	0.73 to 141.60
Jordan	National	25.70 to 130.00
Oman	Sub-national¶	11.01
Saudi Arabia	National	137.61
	Sub-national	6.00 to 149.54
Turkey	Sub-national	11.93 to 49.54
Sub-Saharan Africa		
Chad	Sub-nationalΔ	34.86
Western Europe		
Germany	National	0.03
Greece	Sub-national	4.00 to 32.49
Italy	National	1.40
Central Asia		
Kyrgyzstan	National	88.00
Central and Southern Latin America		
Argentina	Sub-national	12.84
Mexico	Sub-national	25.69
North America		
United States	Sub-national	0.02 to 0.09

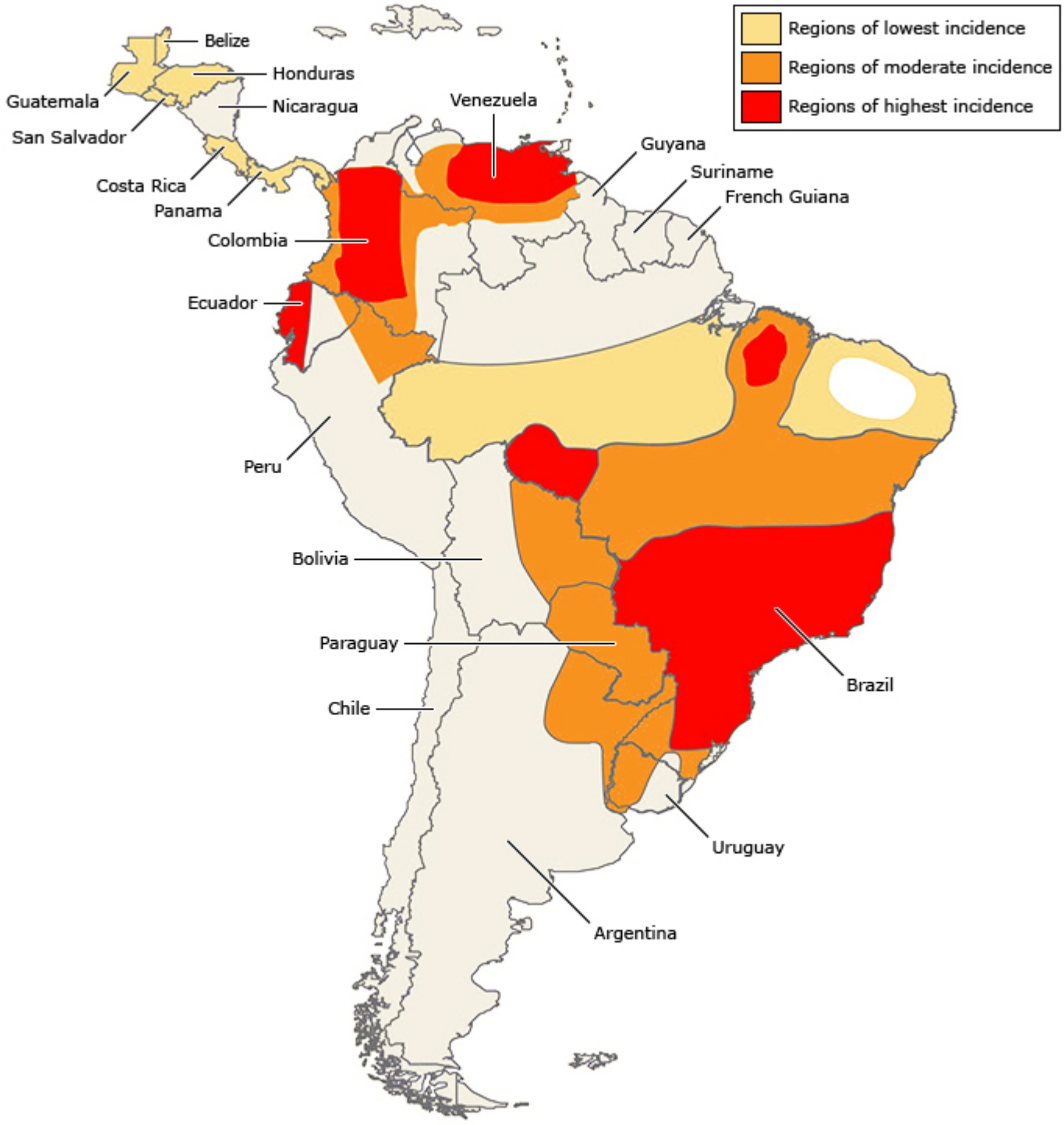
* Includes one study of a nomadic community.

¶ Children only.

Δ Nomadic community.

Graphic 121902 Version 2.0

Distribution of paracoccidioidomycosis by incidence



Distribution of paracoccidioidomycosis in South America.

Graphic 54273 Version 8.0

Differential diagnosis of classic FUO based on symptoms and physical examination

	Infections	Noninfectious inflammatory disorders	Malignancies	Miscellan
Constitutional symptoms and signs				
Triad of night sweats, weight loss, and anorexia	▪ Tuberculosis (pulmonary or extrapulmonary) ▪ Endocarditis ▪ Disseminated mycobacterial infection (miliary tuberculosis, nontuberculous mycobacteria) ▪ Disseminated fungal infection (eg, histoplasmosis, blastomycosis, coccidioidomycosis) ▪ Brucellosis ▪ Typhoid/enteric fever ▪ Q fever ▪ Visceral leishmaniasis	▪ Vasculitis (eg, ANCA-associated, giant-cell arteritis, polyarteritis nodosa)	▪ Lymphoma ▪ Renal cell carcinoma ▪ Metastatic cancer	▪ Castleman ▪ Atrial myxo ▪ Hyperthyro (fever is an uncommon ▪ Tumor necr factor recep associated syndrome (▪ Treatment bladder car intravesicle Calmette-G (BCG) ▪ Hemophag lymphohist
Head and neck				
Headache	▪ Mononucleosis (Epstein-Barr virus, acute HIV syndrome, cytomegalovirus, *Toxoplasma gondii*) ▪ Chronic meningitis (numerous causes) ▪ Typhoid/enteric fever ▪ Acute HIV syndrome	▪ Giant-cell arteritis		▪ Familial Mediterran fever ▪ Pheochrom ▪ Hemolytic-u syndrome ▪ Thrombotic thrombocyt purpura

	▪ Malaria ▪ *Bartonella quintana* infection ▪ Leptospirosis (immune phase of illness) ▪ Scrub typhus ▪ Epidemic typhus ▪ Murine typhus ▪ Q fever ▪ Schistosomiasis ▪ Rat-bite fever			
Temporal artery tenderness		▪ Giant-cell arteritis		
Transient or sustained unilateral vision loss		▪ Giant-cell arteritis (transient visual loss [amaurosis fugax])		
Abnormal fundus exam	▪ Endocarditis (Roth spots) ▪ Tuberculosis (choroid tubercle)	▪ Giant-cell arteritis (transient visual loss [amaurosis fugax])		
Red eye (eg, conjunctivitis, scleritis, uveitis)	▪ Leptospirosis (immune phase of illness) ▪ Murine typhus ▪ Endocarditis (conjunctival petechiae) ▪ Brucellosis ▪ Toxoplasma ▪ Tuberculosis	▪ Adult-onset Still's disease ▪ Vasculitis (rheumatoid, ANCA-associated, polyarteritis nodosa) ▪ Behçet syndrome ▪ Systemic lupus erythematosus		▪ Sarcoidosis ▪ Inflammatc bowel disea ▪ Medication
Sinus symptoms (eg, sinusitis)	▪ Bacterial sinusitis ▪ Dental infections	▪ ANCA-associated vasculitis		▪ Sarcoidosis

Sore throat, pharyngitis	▪ Mononucleosis (Epstein-Barr virus, *Toxoplasma gondii*) ▪ Gonococcal pharyngitis ▪ Rat-bite fever	▪ Adult-onset Still's disease ▪ Giant-cell arteritis ▪ ANCA-associated vasculitis		▪ Sarcoidosis ▪ PFAPA (peri fever with a stomatitis, pharyngitis adenitis) sy ▪ Cyclic neutr
Poor dentition; dental pain	▪ Dental infection ▪ Sinusitis	▪ Giant-cell arteritis (jaw claudication)		
Oral ulcers	▪ Acute HIV syndrome (acute HIV) ▪ Histoplasmosis ▪ Primary herpes simplex infection	▪ Systemic lupus erythematosus ▪ Behçet syndrome ▪ ANCA-associated vasculitis		▪ Crohn's dise ▪ PFAPA (peri fever with a stomatitis, pharyngitis adenitis) sy ▪ Cyclic neutr ▪ Medications
Thyroid enlargement, tenderness, or nodule				▪ Hyperthyro ▪ Subacute th
Lymph nodes				
Localized lymphadenopathy	▪ Mononucleosis (Epstein-Barr virus, acute HIV syndrome [acute HIV], cytomegalovirus, *Toxoplasma gondii*) ▪ Tuberculosis (ie, scrofula) ▪ Cat-scratch disease due to *Bartonella henselae* ▪ Tularemia (typhoidal disease)		▪ Lymphoma ▪ Head and neck cancer ▪ Breast cancer	▪ Kikuchi dise ▪ Castleman ▪ PFAPA (peri fever with a stomatitis, pharyngitis adenitis) sy

Diffuse lymphadenopathy	▪ Mononucleosis (Epstein-Barr virus, acute HIV syndrome [acute HIV], cytomegalovirus, *Toxoplasma gondii*) ▪ Miliary tuberculosis ▪ Scrub typhus ▪ Oroya fever	▪ Systemic lupus erythematosus ▪ Adult-onset Still's disease	▪ Lymphoma ▪ Metastatic disease	▪ Sarcoidosis ▪ Castleman ▪ Medication
Lungs				
Cough +/– hemoptysis	▪ Mycobacterial infection (eg, tuberculosis, *M. kansasii*) ▪ Q fever ▪ Endemic mycoses (eg, histoplasmosis, blastomycosis, coccidioidomycosis) ▪ Schistosomiasis	▪ ANCA-associated vasculitis ▪ Anti-glomerular basement membrane disease ▪ Systemic lupus erythematosus	▪ Lung cancer ▪ Metastases to lung	▪ Pulmonary
Heart				
New or changed murmur	▪ Endocarditis			▪ Atrial myxo
New heart block (first-, second-, or third-degree)	▪ Endocarditis ▪ Lyme disease			
Abdomen				
Abdominal pain	▪ Common intra-abdominal conditions (eg, cholecystitis, appendicitis, diverticulitis) ▪ Viral hepatitis ▪ Liver abscess (WBC, neurtrophilia) ▪ Cholangitis ▪ Typhoid/enteric fever	▪ Behçet syndrome ▪ Vasculitis (eg, polyarteritis nodosa)		▪ Inflammato bowel disea ▪ Splenic infa to vasculitis endocarditi ▪ Hemolytic-u syndrome ▪ Thrombotic thrombocyt purpura ▪ Adrenal insufficienc

	▪ Intra-abdominal abscess ▪ Perihepatitis (Fitz-Hugh-Curtis syndrome in women with pelvic inflammatory disease) ▪ Tuberculosis ▪ Splenic abscess ▪ Coccidioidomycosis ▪ Tularemia ▪ Epidemic typhus ▪ Schistosomiasis ▪ Peritonitis in patient with cirrhosis or on peritoneal dialysis			▪ Complicatic pregnancy ▪ Familial Mediterran fever ▪ Retroperito fibrosis ▪ Mesenteric ▪ Alcoholic he ▪ Tumor necr factor recep associated syndrome (
Diarrhea	▪ Typhoid/enteric fever (constipation is more common) ▪ *Clostridium difficile* infection ▪ Schistosomiasis			▪ Inflammato bowel disea ▪ Medication
Hepatomegaly	▪ Viral hepatitis ▪ Liver abscess (including amoebic) ▪ Extrapulmonary tuberculosis ▪ Disseminated histoplasmosis ▪ Q fever ▪ Acute toxo ▪ Typhoid/enteric fever ▪ Brucellosis ▪ Oroya fever ▪ Schistosomiasis	▪ Adult-onset Still's disease	▪ Hepatocellular carcinoma ▪ Liver metastases ▪ Hepatosplenic T-cell lymphoma	▪ Sarcoidosis ▪ Castleman ▪ Treatment bladder car intravesicle Calmette-G (BCG)

Splenomegaly	▪ Mononucleosis due to Epstein-Barr virus or toxo ▪ Malaria ▪ Endocarditis (may cause splenic abscess) ▪ Disseminated histoplasmosis ▪ Typhoid/enteric fever ▪ *Bartonella quintana* infection ▪ Babesiosis ▪ Brucellosis ▪ Q fever ▪ Schistosomiasis ▪ Visceral leishmaniasis	▪ Systemic lupus erythematosus ▪ Felty syndrome	▪ Lymphoma ▪ Leukemia	▪ Sarcoidosis ▪ Hemophag lymphohist ▪ Castleman
Genitourinary				
Hematuria and/or flank pain	▪ Urinary tract infection ▪ Genitourinary tuberculosis ▪ Endocarditis ▪ Schistosomiasis ▪ Melioidosis	▪ ANCA-related vasculitis ▪ Anti-glomerular basement membrane disease ▪ Systemic lupus erythematosus	▪ Renal cell carcinoma	▪ Hemolytic-u syndrome ▪ Thrombotic thrombocyt purpura ▪ Treatment bladder car intravesicle Calmette-G (BCG)
Pelvic pain	▪ Prostatitis in men (due to enterica gram-negative bacteria, sexually transmitted infections, tuberculosis, blastomycosis, coccidioidomycosis, melioidosis) ▪ Urinary tract infection		▪ Gynecologic, urologic, or colon cancer	▪ Treatment bladder car intravesicle Calmette-G (BCG)

	▪ Gynecologic infection in women, including pelvic inflammatory disease			
Testicular swelling or tenderness	▪ Brucellosis ▪ Genitourinary tuberculosis ▪ Blastomycosis ▪ Coccidioidomycosis ▪ Sexually transmitted infections (eg, gonorrhea) ▪ Epididymitis due to enteric bacteria	▪ Polyarteritis nodosa ▪ Behçet syndrome (genital ulcers most common)		▪ Familial Mediterran fever ▪ Treatment bladder car intravesicle Calmette-G (BCG)
Back				
Back pain	▪ Bacteremia +/– endocarditis ▪ Vertebral osteomyelitis (due to common bacterial causes, brucellosis, tuberculosis, blastomycosis)		▪ Metastatic cancer	
Muscles and joints				
Myalgias	▪ Endocarditis ▪ Acute toxo ▪ *Bartonella quintana* infection (pain in shin bones is common) ▪ Babesiosis ▪ Relapsing fever due to *Borrelia* spp ▪ Leptospirosis ▪ Scrub typhus ▪ Epidemic typhus ▪ Murine typhus ▪ Q fever	▪ Vasculitis (eg, giant-cell arteritis associated with polymyalgia rheumatica) ▪ Systemic lupus erythematosus		▪ Adrenal insufficienc ▪ Familial Mediterran fever ▪ Tumor necr factor recep associated syndrome (▪ Medication

	▪ Schistosomiasis ▪ Rat-bite fever			
Diffuse arthralgias	▪ Brucellosis ▪ Endocarditis ▪ Disseminated gonococcus ▪ Relapsing fever due to *Borrelia* spp ▪ Q fever ▪ Epidemic typhus ▪ Schistosomiasis ▪ Rat-bite fever	▪ Adult-onset Still's disease ▪ Systemic lupus erythematosus ▪ Vasculitis syndromes	▪ Multiple myeloma (pain is localized to back, neck, shoulders, pelvis, hip)	▪ Sarcoidosis ▪ Adrenal insufficienc ▪ Familial Mediterran fever ▪ Medication
Inflammatory arthritis	▪ Septic arthritis ▪ Brucellosis ▪ Parvovirus B19 infection (anemia) ▪ Disseminated gonococcus ▪ Coccidioidomycosis ▪ Chronic meningococcemia (mild leukocytosis, neturophila) ▪ Rat-bite fever	▪ Rheumatoid arthritis ▪ Adult-onset Still's disease ▪ Systemic lupus erythematosus ▪ Behçet syndrome	▪ Paraneoplastic syndrome	▪ Sarcoidosis ▪ Inflammato bowel disea ▪ Crystal-indu arthropathy gout) ▪ Familial Mediterran fever ▪ Medication
Neurologic				
Recent stroke	▪ Endocarditis	▪ Vasculitis (eg, polyarteritis nodosa)		▪ Atrial myxo
Peripheral neuropathy		▪ ANCA-associated vasculitis ▪ Polyarteritis nodosa ▪ Systemic lupus erythematosus		▪ Medication
Skin				
Maculopapular rash	▪ Acute HIV syndrome (acute HIV)	▪ Adult-onset Still's disease (evanescent		▪ Medication

	▪ Typhoid/enteric fever ▪ Mononucleosis due to Epstein-Barr infection (especially after treatment of penicillin) ▪ Scrub typhus ▪ Epidemic typhus ▪ Rat-bite fever	salmon-colored rash during fever) ▪ Systemic lupus erythematosus		
Palpable purpura		▪ Vasculitis (eg, ANCA-associated vasculitis, polyarteritis nodosa)		▪ Medication
Petechiae, splinter hemorrhages	▪ Endocarditis (also can have Osler nodes or Janeway lesions on hands)		▪ Lymphoma ▪ Leukemia	
Erythema nodosum	▪ Streptococcal infection, especially pharyngitis ▪ Tuberculosis ▪ Brucellosis ▪ Endemic mycoses (eg, histoplasmosis, blastomycosis, coccidioidomycosis) ▪ Mononucleosis	▪ Behçet syndrome	▪ Lymphoma ▪ Leukemia ▪ Solid tumors	▪ Sarcoidosis ▪ Inflammato bowel disea ▪ Sweet synd ▪ Drug reacti
Pustules	▪ Disseminated gonococcus ▪ Rickettsialpox ▪ African tick bite fever ▪ Queensland tick typhus	▪ Behçet syndrome		
Mass, nodule, or eschar	▪ Blastomycosis ▪ Coccidioidomycosis ▪ Tularemia ▪ Scrub typhus			▪ Sarcoidosis

	▪ Spotted fever rickettsial infections (other than Rocky Mountain spotted fever) ▪ Melioidosis			

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