Approach to the adult with fever of unknown origin

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INTRODUCTION

Clinicians commonly refer to a febrile illness without an initially obvious etiology (sometimes called fever 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 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 definitions and special populations with FUO as well as the diagnostic approach to the adult with this problem are reviewed here. A specific discussion of the common and uncommon entities causing FUO and the approach to children with FUO is presented separately. (See "Etiologies of fever of unknown origin in adults" and "Fever of unknown origin in children: Evaluation".)

DEFINITION

The definition of FUO derived by Petersdorf and Beeson in 1961 from a prospective analysis of 100 cases has long been the clinical standard [1]:

- Fever higher than 38.3ºC on several occasions
- Duration of fever for at least three weeks
- Uncertain diagnosis after one week of study in the hospital

The definition has been used to compare and contrast FUO in different eras, geographic locales, and special patient populations (table 1A-B) [1-10].

Refinements to the definition have been proposed, including eliminating the in-hospital evaluation requirement because of the increased expense of inpatient care and sophistication of outpatient evaluation [11]. Expansion of the definition has also been suggested to include health care-associated, neutropenic, and HIV-associated fevers that may not be as prolonged [12,13].

Establishing that a patient has an FUO — As noted above, the degree and duration of fever are not the only criteria for defining an FUO. Prior to concluding that a patient has an FUO, the following evaluation should have been performed and should have been unrevealing:

- History
- Physical examination
- Complete blood count, including differential and platelet count
- Blood cultures (three sets drawn from different sites with an interval of at least several hours between each set; in cases in which antibiotics are indicated, all blood cultures should be obtained before administering antibiotics)
- Routine blood chemistries, including liver enzymes and bilirubin
- If liver tests are abnormal, hepatitis A, B, and C serologies
- Urinalysis, including microscopic examination, and urine culture
- Chest radiograph

If any signs or symptoms point to a particular organ system, further testing, imaging, and/or biopsy should be pursued.

ETIOLOGY

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

- Infections
- Malignancies
- Systemic rheumatic diseases (eg, vasculitis, rheumatoid arthritis)

A more detailed description of common and uncommon etiologies of FUO is discussed separately (table 1A and table 1B and table 2). (See "Etiologies of fever of unknown origin in adults".)

EPIDEMIOLOGY

Changes over time — Scientific and technologic advances have greatly refined and expedited the differential diagnosis and therapy of FUO (table 1A-B) [1-9].

- The fraction of undiagnosed FUOs dropped from over 75 percent in the 1930s to less than 10 percent in the 1950s. Since then, the fraction of FUOs that go undiagnosed has steadily increased (figure 1) [4,7,14-16].
- The early FUO series included few systemic rheumatic diseases, illnesses whose characterization has benefited from careful clinical studies, and developments in immunology.
- Extrapulmonary tuberculosis, solid tumors, and abdominal abscesses are now less prevalent causes due to earlier diagnosis by radiologic imaging, particularly computed tomography, and minimally invasive biopsies.
- Exploratory laparotomy has given way to imaging and percutaneous-guided biopsies for diagnosis.
- Infective endocarditis, once a frequent cause of FUO, has become a less common cause with improved techniques for the isolation of organisms. In the current era, when endocarditis is ultimately diagnosed in a patient with FUO, it is more likely to be

culture negative or caused by difficult-to-isolate organisms, such as *Bartonella quintana*. (See "Detection of bacteremia: Blood cultures and other diagnostic tests".)

True FUOs are uncommon. This was illustrated in a report from the Netherlands in which only 73 patients were identified between December 2003 and July 2005 at a 950-bed academic referral hospital and five community hospitals comprising 2800 hospital beds [9]. The authors excluded immunocompromised patients, such as those with AIDS, hypogammaglobulinemia, granulocytopenia, and glucocorticoid therapy. The following distribution of causes was noted:

- Systemic rheumatic disease (eg, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica) – 22 percent
- Infection – 16 percent
- Malignancy – 7 percent
- Miscellaneous – 4 percent
- No diagnosis – 51 percent

Future advances in microbial diagnosis through gene amplification methods and clarification of the pathogenesis of systemic rheumatic diseases will continue to change the distribution of FUO.

Practice advances have not always been helpful in diagnosing FUO. The frequent use of empiric antimicrobials, for example, can delay the diagnosis of some occult abscesses and infections and increases the number of drug fevers. Aggressive immunosuppressive regimens, increased exposure to potentially allergenic medications, lengthy intensive care unit admissions, and the increase in multiresistant organisms as resident hospital flora have all altered the types of FUO's encountered.

Geography — Infectious causes of prolonged fever in resource-limited countries include tuberculosis, typhoid, amebic liver abscesses, and AIDS. Ease of travel has the potential to bring back to the United States and other resource-rich countries more geographically restricted illnesses that may not be familiar to clinicians, such as malaria, brucellosis, kala azar, filariasis, schistosomiasis, African tick bite fever, relapsing fever, Q fever, dengue virus, chikungunya virus, Zika virus, or Lassa fever [17,18]. (See "Evaluation of fever in the returning traveler".)

The classic geographic distribution of some United States zoonoses is also changing, owing to environmental changes such as incursion by humans into formerly unpopulated areas and global warming. Zoonoses like babesiosis, ehrlichiosis, anaplasmosis, and

Lyme disease may present as FUOs in new ecologic niches.

Illnesses contracted abroad may have incubation periods that extend for months; some infections remain latent for years and may therefore present as fevers remote from the time of travel. Individuals traveling may also become infected with organisms to which local residents are not vulnerable because of pre-existing immunity [19].

Despite the wide variety of exotic diseases, the most common infections among series of FUOs have not changed over the past half century. These continue to include typhoid fever, tuberculosis, amebic abscesses, and malaria. Fever of unknown origin is more often caused by an atypical presentation of a common entity than by a rare disorder.

Subpopulations — Different entities figure in the etiology of FUO based upon features of the population being studied.

Age — The causes of FUO vary dramatically with age. In a series of 100 children with FUO, for example, one-third were self-limited undefined viral syndromes [20]. In contrast, multisystem diseases such as systemic rheumatic diseases (including polymyalgia rheumatica, giant cell arteritis, and other vasculitides) and sarcoidosis accounted for 31 percent of cases in a review of patients with FUO over the age of 65 [5]. Infections accounted for 25 percent and neoplasms 12 percent of cases in this report.

AIDS — The causes of FUO in HIV-infected patients reflect the degree of immunosuppression, best measured by CD4 counts and viral load determinations [21]. Acute HIV infection can present as an FUO when telltale symptoms and signs (rash and diffuse adenopathy) are absent. In one series of 79 episodes of FUO among HIV-infected patients with CD4 counts ranging from 0 to 790/microL and a median of 40/microL, 79 percent were due to infections and 8 percent to malignancies; only 9 percent had no definite diagnosis [6]. Over one-half were due to mycobacteria, two-thirds of which were atypical, most commonly *Mycobacterium avium* complex (MAC). Only lymphomas were highly represented among malignancies, particularly non-Hodgkin lymphomas. Disseminated Kaposi's sarcoma was relatively infrequent. A similar distribution was noted in another report of 59 HIV-infected patients [22].

As with FUO in HIV-uninfected patients, the country in which the study is performed influences the prevalent etiologies detected. In one study from Spain, for example, 137 HIV-infected patients with fevers for at least 10 days and no diagnosis after 1 week in hospital underwent bone marrow biopsy [23]. The three most common diagnoses were mycobacterial infection (18 patients with *Mycobacterium tuberculosis* and 14 with MAC), non-Hodgkin lymphoma, and visceral leishmaniasis. (See "Fever and rash in patients with HIV".)

Neutropenia — Neutropenia-associated febrile episodes without a source are most frequently linked to bacteremia. Fungal infections replace bacterial infections in prominence after the acute period (after seven days) [12].

Fever of unknown origin in this population is particularly confounding. It occurs in the context of a serious underlying condition that may itself cause fever. In addition, patients are often taking a number of medications (including antimicrobials), are receiving blood products, have varying degrees of immunosuppression, and, in transplant recipients, may experience allograft rejection. Finally, febrile neutropenia usually mandates empirical antimicrobial therapy, which may confound the subsequent detection of bacterial infections. (See "Overview of neutropenic fever syndromes".)

Fever, even if unexplained, usually abates with return of neutrophils. When fever persists or returns after the patient is no longer neutropenic, hepatosplenic candidiasis should be strongly considered [12]. (See "Chronic disseminated candidiasis (hepatosplenic candidiasis)".)

DIAGNOSTIC APPROACH

The most critical feature of the evaluation of a patient with FUO is to take a careful history and to reassess the patient frequently. It is important to look for uncommon presentations of common diseases and to perform a detailed physical examination.

History and physical examination — The history and physical examination, like laboratory tests, have the potential to generate valuable diagnostic clues in patients with FUO. The art of diagnosis is one of discrimination, as the clinician must determine which data to glean and which clues to pursue. In the series of 73 patients from the Netherlands cited above, the authors found an average of 10.5 potential diagnostic clues per patient through their careful history and physical examination and three per patient through laboratory testing [9]. Eighty-one percent of these clues were misleading.

A thorough history should include the following information:

- Travel
- Animal exposure (eg, pets, occupational, living on a farm)
- Immunosuppression (with the degree noted)
- Drug and toxin history, including antimicrobials

- Localizing symptoms

Subtle findings may be elicited through a careful history. Examples include subtle changes in behavior or cognition consistent with granulomatous meningitis, jaw claudication consistent with giant cell arteritis, tooth sensitivity to cold or gum tenderness consistent with dental abscesses, and nocturia consistent with prostatitis. Revisiting the history on several occasions may provide new clues in difficult cases.

The degree of fever, nature of the fever curve, apparent toxicity, and response to antipyretics has **not** been found to provide enough specificity to guide the diagnosis of FUO [24]. Fever may be attenuated in older patients and moderated by use of steroids and nonsteroidal anti-inflammatory drugs. However, the course of the fever curve may be helpful in determining whether the disease is escalating or waning.

Diagnostic testing — A wide variety of diagnostic tests may be useful in FUO. In addition to the evaluation to establish the presence of an FUO (see 'Establishing that a patient has an FUO' above), we recommend the following minimum diagnostic evaluation:

- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
- Serum lactate dehydrogenase
- Tuberculin skin test or interferon-gamma release assay (see "Use of interferon-gamma release assays for diagnosis of latent tuberculosis infection (tuberculosis screening) in adults")
- HIV immunoassay and HIV viral load for patients at high risk (see "Acute and early HIV infection: Clinical manifestations and diagnosis", section on 'Diagnosis')
- Three routine blood cultures drawn from different sites over a period of at least several hours without administering antibiotics, if not already performed
- Rheumatoid factor
- Creatine phosphokinase

- Heterophile antibody test in children and young adults
- Antinuclear antibodies
- Serum protein electrophoresis
- Computed tomography (CT) scan of abdomen
- CT scan of chest

Test performance — For most of these tests, the false-positive rate, which can lead to unnecessary investigations, is similar to the rate of a helpful result. This was illustrated in the series cited above of 73 patients from the Netherlands seen between December 2003 and July 2005 [9]:

- Chest radiograph – Performed in 73 patients: helpful in 6 and false positive in 8 (8 and 11 percent, respectively)
- Chest CT – Performed in 46 patients: helpful in 9 and false positive in 8 (20 and 17 percent, respectively)
- Abdominal CT – Performed in 60 patients: helpful in 12 and false positive in 17 (20 and 28 percent, respectively)
- Positron emission tomography scan – Performed in 70 patients: helpful in 23 and false positive in 10 (33 and 14 percent, respectively)

Acute-phase reactants — Most clinicians favor obtaining an ESR or CRP, despite their lack of specificity. One study reviewed ESR elevations above 100 mm/h among 263 patients with FUO: 58 percent had malignancy, most commonly lymphoma, myeloma, or metastatic colon or breast cancer, and 25 percent had infections such as endocarditis or systemic rheumatic diseases like rheumatoid arthritis or giant cell arteritis [25].

Measurement of the ESR seems to have its greatest use in establishing a serious underlying cause of FUO, although drug hypersensitivity reactions, thrombophlebitis, and renal disease, particularly the nephrotic syndrome, may be accompanied by a very high ESR in the absence of infection or malignancy. (See "Acute phase reactants".)

A normal ESR or CRP also suggests that a significant inflammatory process, of whatever origin, is absent. Once again, however, there are exceptions. As an example, some patients with giant cell arteritis have a normal ESR [26].

Procalcitonin, a serum biomarker that is elevated with certain bacterial infections, has no clear role in distinguishing between bacterial infections and other causes of FUO, and we do not recommend checking it as part of the FUO evaluation.

CT scanning — We recommend an abdominal and chest CT as part of the routine evaluation of FUO. As noted above, however, the rate of false-positive tests with these modalities is similar to the rate of a true positive result [9]. (See 'Test performance' above.)

CT scanning of the abdomen has nearly replaced exploratory laparotomy and other radiographic tests in the search for occult abscesses or hematomas in patients with FUO. The finding of abdominal lymphadenopathy can be a clue to lymphoma or a granulomatous process. The usefulness of CT has resulted in this examination being used in nearly all patients with FUO. While magnetic resonance imaging scan can be more sensitive in certain settings (eg, the diagnosis of spinal epidural abscess), it is rarely required in the initial evaluation of FUO.

For similar reasons, CT scanning of the chest is invaluable in the identification of small nodules (indicative of fungal, mycobacterial, or nocardial infection or malignancy). The identification of hilar or mediastinal adenopathy may prompt biopsy by mediastinoscopy, providing a diagnosis of lymphoma, histoplasmosis, or sarcoidosis.

Nuclear medicine testing — Nuclear medicine testing is a more controversial area in the diagnosis of FUO. We generally reserve nuclear medicine imaging for cases in which the initial evaluation (including abdominal and chest CT) remains negative and a screening look at the entire body is desired. As noted above, however, a positive result is almost as likely to be a false positive as it is to be a true positive [9]. (See 'Test performance' above.)

Both gallium-67– and indium-111–labeled leukocyte scanning are highly sensitive by virtue of including the whole body. Neither study, however, can pinpoint a diagnosis; as a result, they are nonspecific tests to localize a site for more specific evaluation such as with CT. When studied, the overall yield of gallium-67– or indium-111–labeled leukocyte scanning may be higher than with CT or ultrasound, since the latter tests focus on only a few parts of the body [27,28]. In one study of 145 cases of FUO, for example, 29 percent of the gallium-67 scans were helpful in establishing a diagnosis, versus 6 and 14 percent of ultrasound examinations and CT scans, respectively [27].

A review of FUO in older adults found that gallium scanning had a diagnostic contribution in 17 of 47 cases, while 11 were thought to be false positives [5]. This study recommended gallium scanning as the next step after routine laboratory tests, temporal artery biopsy, and abdominal ultrasonography in this population.

F-fluorodeoxyglucose positron emission tomography (FDG-PET) appears to be very sensitive in identifying anatomic sites of inflammation and malignancy. This modality may find a valuable place in the evaluation of FUO [29-31], but additional data are needed to determine its added value beyond repeated clinical evaluation over time and routine CT.

Other tests — When the history, examination, or imaging suggests a possible source, specific testing should be performed. Examples include:

- Subtle central nervous system symptoms or signs should prompt a lumbar puncture and imaging of the head and/or spine.
- In the United States, a travel history to the Midwest or the deserts of the West should raise the question of a fungal process like histoplasmosis or coccidioidomycosis, respectively. Testing for the suspected fungal pathogen in individuals who have resided in an endemic area can be useful. (See "Diagnosis and treatment of pulmonary histoplasmosis" and "Diagnosis and treatment of disseminated histoplasmosis in HIV-uninfected patients" and "Coccidioidomycosis: Laboratory diagnosis and screening".)
- Individuals who have recently visited or resided in a malaria-endemic region should have blood sent for a thick and thin smear. (See "Laboratory tools for diagnosis of malaria".)
- Other appropriate tests for returning travelers are discussed separately. (See "Evaluation of fever in the returning traveler".)
- A history of trauma, adjacent infection or intravenous drug use may suggest thrombophlebitis of the legs, arms, or pelvic vessels. Venous duplex imaging can be diagnostic. Fever usually responds to anticoagulation within several days.

Biopsy — Biopsy is a critical modality in the directed (as opposed to screening) evaluation of FUO. The following examples include data from the Netherlands study of 73 patients cited above on the utility of biopsy of different sites [9]:

- Liver biopsy for possible miliary tuberculosis, granulomatous hepatitis, or other granulomatous diseases such as sarcoidosis – Liver biopsy was performed in 7 patients; it was helpful in 1 and false positive in 3.

- Lymph node biopsy for possible malignancy, especially lymphoma, or infections such as cat-scratch disease – Lymph node biopsy was performed in 11 patients; it was helpful in 5 and false positive in 3.
- Temporal artery to look for giant cell arteritis or biopsy of an affected tissue to diagnose a vasculitic process such as polyarteritis nodosa – Temporal artery biopsy was performed in 14 patients; it was helpful in 1 with no false positives.
- Pleural or pericardial biopsy in the evaluation of extrapulmonary tuberculosis.
- Bone marrow biopsy was performed in 19 patients; it was helpful in 2 and false positive in 1.

Two retrospective reviews of bone marrow biopsies to evaluate FUOs demonstrated high diagnostic yields and high prevalence of hematologic malignancies [32,33]. The authors did not define the prevalence of infectious diseases at the hospitals under study nor did they define the decision-making that led physicians to request bone marrow biopsies. However, the observations in both studies were similar: lymphomas constituted >40 percent of diagnoses, whereas infections were detected in <15 percent of patients. Other causes of FUO included acute myeloid leukemia, myelodysplastic syndromes, sarcoidosis, systemic mastocytosis, and disseminated granulomatosis. In both studies, hematologic malignancies were strongly predicted by the presence of leukoerythroblastic changes in peripheral blood and a greatly elevated ferritin level (>1000 ng/mL); in one of the studies, hematologic malignancies were also predicted by the presence of splenomegaly [33].

Therapeutic trials — Therapeutic trials of antimicrobials or glucocorticoids, while tempting in the effort to "do something," rarely establish a diagnosis. In addition, the diagnostic yield of blood cultures and cultures of biopsy material will be reduced following the initiation of antibiotics. Antimicrobial agents could be expected to suppress, but not cure, many infectious processes such as an occult abscess since adjunctive drainage would usually be required.

Antibiotics can have effects on other infections than the ones to which therapy is directed. Rifampin, for example, used in a therapeutic trial for tuberculosis may suppress staphylococcal osteomyelitis or diminish the ability to detect difficult-to-isolate organisms causing endocarditis. The appropriate duration of a therapeutic trial is also unclear since a number of infections such as endocarditis or pelvic inflammatory disease can take as much as one week for fever to abate, even with appropriate therapy. Empiric antibiotics should never be started solely to treat fever.

A therapeutic trial of glucocorticoids for an inflammatory process should not replace relevant biopsies for steroid-responsive diseases such as sarcoidosis, other granulomatous diseases, or vasculitis. A careful evaluation for infection should precede such a trial.

Emergent FUO therapy — When morbid illnesses like endocarditis, temporal arteritis, central nervous system tuberculosis, and leptospirosis present as FUOs, they rarely progress rapidly enough to warrant emergent treatment. However, when illnesses like these are suspected, we speed diagnostic testing and treat empirically.

Antipyretics improve patients' comfort, reducing headache, myalgias, arthralgias, and fatigue. However, drugs with antipyretic effects may delay or obscure early symptoms and signs of specific diseases. Thus, we try to avoid prescribing acetaminophen, nonsteroidal anti-inflammatory drugs, or glucocorticoids.

The use of antipyretics is discussed in greater detail separately. (See "Pathophysiology and treatment of fever in adults", section on 'Treatment of fever and hyperthermia'.)

No diagnosis — The rate of no diagnosis in studies of FUO published since 1990 has varied widely from 9 to 51 percent [4-9]. As described in the following section, most of these patients do well.

OUTCOME

The outcome of patients with an FUO depends upon the underlying diagnosis and any comorbid conditions. Among children with FUO, 88 percent of those caused by infections have no sequelae.

Most adults who remain undiagnosed after an extensive evaluation also have a good prognosis [7,8,34]. This was illustrated in a study of 199 patients with FUO, 61 of whom (30 percent) were discharged from the hospital without a diagnosis [34].

- A definite diagnosis was established in 12 (20 percent), usually within two months after discharge.
- Thirty-one (51 percent) became symptom-free during hospitalization or shortly following discharge.
- Eighteen (30 percent) had persisting or recurring fever for several months or even years after discharge, 10 of whom were considered to be finally cured.

- Four were treated with glucocorticoids and six required intermittent therapy with nonsteroidal anti-inflammatory drugs.
- Six died, but the cause of death was considered to be related to the disease that caused FUO in only two cases.

Similar findings were noted in the Netherlands series of 73 patients cited above [9]. Among the 37 patients with no diagnosis who were followed for at least six months, 16 spontaneously recovered, 5 recovered with nonsteroidal anti-inflammatory drugs or glucocorticoids, 15 had persistent fever, and 1 died.

SUMMARY AND RECOMMENDATIONS

- Fever of unknown origin (FUO) is defined as fever higher than 38.3ºC on several occasions lasting for at least three (some use two) weeks without an established etiology despite intensive evaluation and diagnostic testing. (See 'Definition' above.)
- Three general categories of illness account for the majority of "classic" FUO cases and have been consistent through the decades. These categories are infections, malignancies, and systemic rheumatic diseases. (See 'Etiology' above.)
- The incidence of specific etiologic agents of FUO varies by age of the population, by potential exposure to infectious agents, by host susceptibility to infection, and over time with advances in diagnostics in identifying the etiologic agent. (See 'Epidemiology' above.)
- The most important aspects of the evaluation of a patient with FUO are to take a meticulous history, perform a detailed physical examination, and to reassess the patient frequently. (See 'History and physical examination' above.)
- We recommend the following minimum diagnostic evaluation: blood cultures, erythrocyte sedimentation rate or C-reactive protein, serum lactate dehydrogenase, HIV antibody test and viral load, rheumatoid factor, heterophile antibody test, creatine phosphokinase, antinuclear antibodies, tuberculin skin test or interferon-gamma release assay, serum protein electrophoresis, and computed tomography scan of abdomen and chest. (See 'Diagnostic testing' above.)
- The primary evaluation and diagnostic workup may suggest an appropriate site for biopsy that could establish the diagnosis. (See 'Biopsy' above.)

- The diagnostic evaluation may fail to identify an etiology in as many as 30 to 50 percent of patients. Most adults who remain undiagnosed have a good prognosis. (See 'Outcome' above.)

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GRAPHICS

Case studies of fever of unknown origin

Author	Alt	Petersdorf	Vanderschueren	Miller	Knockaert	Bleeker-Rovers	Fusco
Years	1913 to 1930	1952 to 1959	1990 to 1999	1989 to 1993	1980 to1989	2003 to 2005	2005 to 2015
Location	Boston, United States	Seattle, United States	Belgium	London, United Kingdom	Belgium	Netherlands	Asia, Europe, Middle East
Subpopulation	Adults	Adults	Adults	AIDS	Elderly	Adults¶	Adults
Case definition*	1	2	2	2	2	2	Varies$^{\Delta}$
Number of cases	101	100	290	79	47	73	3164
Diagnostic categories◇							
Infections	11	36	20	80	25	16	38
Neoplasms	6	19	10	8	12	7	12
Multisystem§	0	17	24	1	31	22	21
Miscellaneous	6	21	13	2	20	4	6
No diagnosis	78	7	34	9	12	51	23

* 1: no diagnosis at time of hospital discharge; 2: temp >101°F (38.3°C), duration >3 weeks, undiagnosed >1 week; 3: temp >101.3°F (38.5°C), duration >2 weeks, undiagnosed.

¶ Immunocompromised excluded.

Δ Systemic review of 18 case series that were written in English and appeared between 2005 to 2015.

◇ Numbers represent percentages.

§ Includes collagen vascular disorders (eg, systemic lupus erythematosus, rheumatoid arthritis, and vasculitis), and granulomatous diseases (eg, sarcoidosis).

Data from:

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Graphic 54701 Version 7.0

Case studies of fever of unknown origin: prevalent diagnoses

Diagnosis	Case study					
	Alt 1913 to 1930 n = 23	**Petersdorf 1952 to 1959 n = 93**	**de Kleijn 1992 to 1994 n = 117**	**Vanderschueren 1990 to 1999 n = 192**	**Miller 1989 to 1993 n = 72**	**Knockaert 1980 to 1989 n = 41**
Location	Boston, United States	Seattle, United States	Netherlands	Belgium	London, United Kingdom	Belgium
Rheumatic fever	2	6	0	0	0	0
Abdominal abscess	1	4	4	5	0	5
Endocarditis	0	5	4	11	0	2
Syphilis	1	1	1	0	0	0
Mycobacterial	6	12	3	8	57	15
Lymphoma	2	8	11	14	7	5
Solid tumor	3	10	7	7	1	7
Sarcoid	0	2	2	10	0	2
Lupus	0	5	2	8	0	0
Rheumatoid arthritis	0	0	2	2	0	5
Giant cell arteritis	0	2	4	11	0	19
Drug fever	0	1	3	4	0	7
Factitious fever	0	3	2	1	3	0

Numbers represent number of cases.

Alt H, et al. JAMA 1930; 94:1457. Petersdorf RG. Arch Intern Med 1992; 152:21. de Kleijn EM, et al. Medicine (Baltimore) 1997; 76:392. Vanderschueren S, et al. Arch Intern Med 2003; 163:1033. Miller RF, et al. Int J STD AIDS 1996; 7:170. Knockaert DC, et al. Clin Infect Dis 1994; 18:601.

Graphic 66395 Version 5.0

Less common diagnoses of fever of unknown origin

Infections
Abscesses (especially intra-abdominal)
African tick bite fever*
Amebic liver abscess*
Anaplasmosis/ehrichiosis*
Babesiosis*
Brucellosis*
Castleman's disease
Chikungunya*
Chronic active hepatitis
Culture-negative endocarditis¶
Cytomegalovirus
Dental abscesses
Dengue*
Diskitis
Epididymitis
Fascioloiasis*
Filariasis*
Gonococcal arthritis
Herpes simplex encephalitis
Infectious mononeucleosis
Kala azar (visceral leishmaniasis)*
Kikuchi's disease
Lassa fever*
Leptospirosis*
Lyme disease*
Osteomyelitis
Prostatitis
Pyelonephritis

Malignancies
Aleukemic leukemia
Atrial myxoma
Colon cancer
Hepatocellular carcinoma or other tumors metastatic to the liver
Kaposi's sarcoma
Leukemia
Lung cancer
Lymphoma, especially non-Hodgkin's
Mesothelioma
Multiple myeloma
Myelodysplastic syndromes
Renal cell carcinoma
Sarcoma

Systemic inflammatory diseases
Allergic granulomatous angiitis
Antiphospholipid syndrome
Behçet's disease
Cryoglobulinemia
Giant cell arteritis
Granulomatosis with polyangiitis (formerly Wegener's disease)
Granulomatous hepatitis
Hypersensitivity vasculitis
Inflammatory bowel disease
Panaortitis
Polyarteritis nodosa
Polymyalgia rheumatica
Reactive arthritis (formerly Reiter's syndrome)
Sarcoidosis
Still's disease
Systemic lupus erythematosis
Takayasu's arteritis

Miscellaneous
Disorders of temperature regulation (neurologic and dermatologic)
Drug fever$^{\Delta}$
Environmental (metal and polymer fume fevers)
Factitious fever
Familial Mediterranean fever
Inflammatory bowel disease
Neuroleptic malignant syndrome
Periodic fever
Pulmonary emboli
Retroperitoneal hematomas
Chronic fatigue syndrome
Thyroiditis

Pyometria
Q fever*
Relapsing fever (*Borrelia recurrentis*)*
Rheumatic fever
Sinusitis
Toxoplasmosis
Typhoid fever*
Tuberculosis
Whipple's disease
Zika virus*

More common causes are in **bold type**.

* Travel and environmental exposure histories are especially relevant.

¶ Causes include *Actinobacillus* spp, *Bartonella* spp, *Brucella* spp, *Cardiobacterium* spp, *Chlamydia* spp, *Coxiella burnetii*, *Eikenella* spp, *Haemophilus* spp, *Histoplasma capsulatum*, *Kingella* spp, *Legionella* spp, *Mycoplasma* spp, *Tropheryma whipplei*, and marantic endocarditis.

Δ Antimicrobials (especially sulfonamides and penicillins), antiepileptic, antithyroid, and nonsteroidal anti-inflammatory drugs.

Graphic 62509 Version 7.0

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

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

Graphic 73878 Version 3.0

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