Chapter 20: Fever of Unknown Origin

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INTRODUCTION

DEFINITION

Clinicians commonly refer to any febrile illness without an initially obvious etiology as *fever of unknown origin* (FUO). Most febrile illnesses either resolve before a diagnosis can be made or develop distinguishing characteristics that lead to a diagnosis. The term *FUO* should be reserved for prolonged febrile illnesses without an established etiology despite intensive evaluation and diagnostic testing. This chapter focuses on FUO in the adult patient.

FUO was originally defined by Petersdorf and Beeson in 1961 as an illness of >3 weeks' duration with fever of ≥38.3°C (≥101°F) on two occasions and an uncertain diagnosis despite 1 week of inpatient evaluation. Nowadays, most patients with FUO are hospitalized only if their clinical condition requires it, and not for diagnostic purposes alone; thus the in-hospital evaluation requirement has been eliminated from the definition. The definition of FUO has been further modified by the exclusion of immunocompromised patients, whose workup requires an entirely different diagnostic and therapeutic approach. For optimal comparison of patients with FUO in different geographic areas, it has been proposed that the quantitative criterion (diagnosis uncertain after 1 week of evaluation) be changed to a qualitative criterion that requires the performance of a specific list of investigations. Accordingly, FUO is now defined as follows:

1. Fever ≥38.3°C (≥101°F) on at least two occasions
2. Illness duration of ≥3 weeks
3. No known immunocompromised state
4. Diagnosis that remains uncertain after a thorough history-taking, physical examination, and the following obligatory investigations: determination of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level; platelet count; leukocyte count and differential; measurement of levels of hemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibodies, and rheumatoid factor; protein electrophoresis; urinalysis; blood cultures ($n = 3$); urine culture; chest x-ray; abdominal ultrasonography; and tuberculin skin test (TST) or interferon γ release assay (IGRA).

Closely related to FUO is *inflammation of unknown origin (IUO)*, which has the same definition as FUO, except for the body temperature criterion: IUO is defined as the presence of elevated inflammatory parameters (CRP or ESR) on multiple occasions for a period of at least 3 weeks in an immunocompetent patient with normal body temperature, for which a final explanation is lacking despite history-taking, physical examination, and the obligatory tests listed above. It has been shown that the causes and workup for IUO are the same as for FUO. Therefore, for convenience, the term FUO will refer to both FUO and IUO within the remainder of this chapter.

ETIOLOGY AND EPIDEMIOLOGY

Table 20-1 summarizes the findings of large studies on FUO conducted over the past 20 years.

TABLE 20-1

Etiology of FUO: Pooled Results of Large Studies Published in the Past 20 Years (1999–2019)

GEOGRAPHIC AREA	NO. OF COHORTS (INCLUSION PERIOD)	NO. OF PATIENTS	INFECTIONS, MEDIAN % (RANGE)	NONINFECTIOUS INFLAMMATORY DISEASES, MEDIAN % (RANGE)	MALIGNANCY, MEDIAN % (RANGE)	MISCELLANEOUS, MEDIAN % (RANGE)	NO DIAGNOSIS, MEDIAN % (RANGE)
Western Europe	10 (1990–2014)	1820	17 (11–32)	25 (12–32)	10 (3–20)	10 (0–15)	37 (26–51)
Other European and Turkey	13 (1984–2015)	1316	38 (26–59)	25 (15–38)	14 (5–19)	6 (2–18)	16 (4–35)
Middle East	3 2009–2010 and ?[a]	1235	66 (42–79)	15 (7–17)	7 (1–30)	1 (0–12)	8 (2–12)
Asia	20 (1994–2017)	3802	42 (11–58)	20 (7–57)	13 (6–22)	9 (0–15)	18 (0–36)

[a]One study (published in 2015) did not report the inclusion period.

Abbreviation: NIID, non-infectious inflammatory disease.

For references, see supplementary material at www.accessmedicine.com/harrisons

The range of FUO etiologies has evolved since its first definition as a result of changes in the spectrum of diseases causing FUO, the widespread use of antibiotics, and especially the availability of new diagnostic techniques. The proportion of cases caused by intraabdominal abscesses and tumors, for example, has decreased because of earlier detection by CT and ultrasound. In addition, infective endocarditis is a less frequent cause because blood culture and echocardiographic techniques have improved. Conversely, some diagnoses such as acute HIV infection were unknown six decades ago.

Roughly comparable to 60 years ago, in non-Western cohorts infections remain the most common cause of FUO. Up to half of all infections in patients with FUO outside Western nations are caused by *Mycobacterium tuberculosis*, which is a less common cause in Western Europe and probably also in the United States. Recent data from the latter, however, have not been reported. In Western cohorts, noninfectious inflammatory diseases (NIIDs), including autoimmune, autoinflammatory, and granulomatous diseases, as well as vasculitides, form the most common cause of FUO. More than one-third of Western patients with FUO have a diagnosis that falls within the category of NIIDs. The number of FUO patients diagnosed with NIIDs probably will not decrease in the near future, as fever may precede more typical manifestations or laboratory evidence of these diseases by months. Moreover, many NIIDs can be diagnosed only after prolonged observation and exclusion of other diseases.

In Western cohorts, FUO remains unexplained in more than one-third of patients. This is much higher than 60 years ago. This difference can be explained by the fact that in patients with fever a diagnosis is often established before 3 weeks have elapsed because these patients tend to seek medical advice earlier, and because better diagnostic techniques, such as CT, MRI, and positron emission tomography (PET)/CT, are now available. Therefore, only the cases that are most difficult to diagnose continue to meet the criteria for FUO. Furthermore, most patients who have FUO without a diagnosis currently do well. A less aggressive diagnostic approach may be used in clinically stable patients once diseases with immediate therapeutic or prognostic consequences have been ruled out. In patients with recurrent fever (defined as repeated episodes of fever interspersed with fever-free intervals of at least 2 weeks and apparent remission of the underlying disease), the chance of attaining an etiologic diagnosis is <50%.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for FUO is extensive. It is important to remember that FUO is far more often caused by an atypical presentation of a rather common disease than by a very rare disease. **Table 20-2** presents an overview of possible causes of FUO. Atypical presentations of endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmonary tuberculosis are the more common infectious disease diagnoses. Q fever and Whipple's disease (*Tropheryma whipplei* infection) are quite rare but should always be kept in mind as a cause of FUO since the presenting symptoms can be nonspecific. Serologic testing for Q fever, which results from exposure to animals or animal products, should be performed by immunofluorescence assay (IFA) when the patient lives in a rural area or has a history of heart valve disease, an aortic aneurysm, or a vascular prosthesis. In patients with unexplained symptoms localized to the central nervous system, gastrointestinal tract, or joints, polymerase chain reaction testing for *Tropheryma whipplei* should be performed. Travel to or (former) residence in tropical countries or the American Southwest should lead to consideration of infectious diseases such as malaria, leishmaniasis, histoplasmosis, or coccidioidomycosis. Fever with signs of endocarditis and negative blood culture results poses a special problem. Culture-negative endocarditis **(Chap. 128)** may be due to difficult-to-culture bacteria such as nutritionally variant bacteria, HACEK organisms (including *Haemophilus parainfluenzae*, *H. paraphrophilus*, *Aggregatibacter actinomycetemcomitans*, *A. aphrophilus*, *A. paraphrophilus*, *Cardiobacterium hominis*, *C. valvarum*, *Eikenella corrodens*, and *Kingella kingae*; discussed below), *Coxiella burnetii*, *T. whipplei*, and *Bartonella* species. Marantic endocarditis is a sterile thrombotic disease that occurs as a paraneoplastic phenomenon, especially with adenocarcinomas. Sterile endocarditis is also seen in the context of systemic lupus erythematosus and antiphospholipid syndrome.

TABLE 20-2

All Reported Causes of Fever of Unknown Origin (FUO)[a]

Infections	
Bacterial, nonspecific	Abdominal abscess, adnexitis, apical granuloma, appendicitis, cholangitis, cholecystitis, diverticulitis, endocarditis, endometritis, epidural abscess, infected joint prosthesis, infected vascular catheter, infected vascular prosthesis, infectious arthritis, infective myonecrosis, intracranial abscess, liver abscess, lung abscess, malakoplakia, mastoiditis, mediastinitis, mycotic aneurysm, osteomyelitis, pelvic inflammatory disease, prostatitis, pyelonephritis, pylephlebitis, renal abscess, septic phlebitis, sinusitis, spondylodiscitis, xanthogranulomatous urinary tract infection
Bacterial, specific	Actinomycosis, atypical mycobacterial infection, bartonellosis, brucellosis, *Campylobacter* infection, *Chlamydia pneumoniae* infection, chronic meningococcemia, ehrlichiosis, gonococcemia, legionellosis, leptospirosis, listeriosis, louse-borne relapsing fever (*Borrelia recurrentis*), Lyme disease, melioidosis (*Pseudomonas pseudomallei*), *Mycoplasma* infection, nocardiosis, psittacosis, Q fever (*Coxiella burnetii),* rickettsiosis, *Spirillum minor* infection, *Streptobacillus moniliformis* infection, syphilis, tick-borne relapsing fever (*Borrelia duttonii*), tuberculosis, tularemia, typhoid fever and other salmonelloses, Whipple's disease (*Tropheryma whipplei*), yersiniosis
Fungal	Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, *Malassezia furfur* infection, paracoccidioidomycosis, *Pneumocystis jirovecii* pneumonia, sporotrichosis, zygomycosis
Parasitic	Amebiasis, babesiosis, echinococcosis, fascioliasis, malaria, schistosomiasis, strongyloidiasis, toxocariasis, toxoplasmosis, trichinellosis, trypanosomiasis, visceral leishmaniasis
Viral	Colorado tick fever, coxsackievirus infection, cytomegalovirus infection, dengue, Epstein-Barr virus infection, hantavirus infection, hepatitis (A, B, C, D, E), herpes simplex, HIV infection, human herpesvirus 6 infection, parvovirus infection, West Nile virus infection
Noninfectious Inflammatory Diseases	
Systemic rheumatic and autoimmune diseases	Ankylosing spondylitis, antiphospholipid syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behçet's disease, cryoglobulinemia, dermatomyositis, Felty syndrome, gout, mixed connective-tissue disease, polymyositis, pseudogout, reactive arthritis, relapsing polychondritis, rheumatic fever, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome

Vasculitis	Allergic vasculitis, eosinophilic granulomatosis with polyangiitis, giant cell vasculitis/polymyalgia rheumatica, granulomatosis with polyangiitis, hypersensitivity vasculitis, Kawasaki disease, polyarteritis nodosa, Takayasu arteritis, urticarial vasculitis
Granulomatous diseases	Idiopathic granulomatous hepatitis, sarcoidosis
Autoinflammatory syndromes	Adult-onset Still's disease, Blau syndrome, CAPS[b] (cryopyrin-associated periodic syndromes), Crohn's disease, DIRA (deficiency of the interleukin 1 receptor antagonist), familial Mediterranean fever, hemophagocytic syndrome, hyper-IgD syndrome (HIDS, also known as mevalonate kinase deficiency), juvenile idiopathic arthritis, PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne), PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis), recurrent idiopathic pericarditis, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis), Schnitzler syndrome, TRAPS (tumor necrosis factor receptor–associated periodic syndrome)
Neoplasms	
Hematologic malignancies	Amyloidosis, angioimmunoblastic lymphoma, Castleman's disease, Hodgkin's disease, hypereosinophilic syndrome, leukemia, lymphomatoid granulomatosis, malignant histiocytosis, multiple myeloma, myelodysplastic syndrome, myelofibrosis, non-Hodgkin's lymphoma, plasmacytoma, systemic mastocytosis, vaso-occlusive crisis in sickle cell disease
Solid tumors	Most solid tumors and metastases can cause fever. Those most commonly causing FUO are breast, colon, hepatocellular, lung, pancreatic, and renal cell carcinomas.
Benign tumors	Angiomyolipoma, cavernous hemangioma of the liver, craniopharyngioma, necrosis of dermoid tumor in Gardner's syndrome
Miscellaneous Causes	
	ADEM (acute disseminated encephalomyelitis), adrenal insufficiency, aneurysms, anomalous thoracic duct, aortic dissection, aortic-enteral fistula, aseptic meningitis (Mollaret's syndrome), atrial myxoma, brewer's yeast ingestion, Caroli disease, cholesterol emboli, cirrhosis, complex partial status epilepticus, cyclic neutropenia, drug fever, Erdheim-Chester disease, extrinsic allergic alveolitis, Fabry's disease, factitious disease, fire-eater's lung, fraudulent fever, Gaucher disease, Hamman-Rich syndrome (acute interstitial pneumonia), Hashimoto's encephalopathy, hematoma, hypersensitivity pneumonitis, hypertriglyceridemia, hypothalamic hypopituitarism, idiopathic normal-pressure hydrocephalus, inflammatory pseudotumor, Kikuchi's disease, linear IgA dermatosis, mesenteric fibromatosis, metal fume fever, milk protein allergy, myotonic dystrophy, nonbacterial osteitis, organic dust toxic syndrome, panniculitis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes), polymer fume fever, post–cardiac injury syndrome, primary biliary cirrhosis, primary hyperparathyroidism, pulmonary embolism, pyoderma gangrenosum, retroperitoneal fibrosis, Rosai-Dorfman disease, sclerosing mesenteritis, silicone embolization, subacute thyroiditis (de Quervain's), Sweet syndrome (acute febrile neutrophilic dermatosis), thrombosis, tubulointerstitial nephritis and uveitis syndrome (TINU), ulcerative colitis
Thermoregulatory Disorders	
Central	Brain tumor, cerebrovascular accident, encephalitis, hypothalamic dysfunction
Peripheral	Anhidrotic ectodermal dysplasia, exercise-induced hyperthermia, hyperthyroidism, pheochromocytoma

[a]This table includes all causes of FUO that have been described in the literature.

[b]CAPS includes chronic infantile neurologic cutaneous and articular syndrome (CINCA, also known as neonatal-onset multisystem inflammatory disease, or NOMID), familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome.

Of the NIIDs, adult-onset Still's disease, large-vessel vasculitis, polymyalgia rheumatica, systemic lupus erythematodus (SLE), and sarcoidosis are rather common diagnoses in patients with FUO. The hereditary autoinflammatory syndromes are very rare (with the exception of familial Mediterranean fever in specific geographic regions) and usually present in young patients. Schnitzler syndrome, which can present at any age, is uncommon but can often be diagnosed easily in a patient with FUO who presents with urticaria, bone pain, and monoclonal gammopathy.

Although most tumors can present with fever, malignant lymphoma is by far the most common diagnosis of FUO among the neoplasms. Sometimes the fever even precedes lymphadenopathy detectable by physical examination.

Apart from drug-induced fever and exercise-induced hyperthermia, none of the miscellaneous causes of fever is found very frequently in patients with FUO. Virtually all drugs can cause fever, even after long-term use. *Drug-induced fever*, including DRESS (drug reaction with eosinophilia and systemic symptoms; **Fig. A1-48**), is often accompanied by eosinophilia and also by lymphadenopathy, which can be extensive. More common causes of drug-induced fever are allopurinol, carbamazepine, lamotrigine, phenytoin, sulfasalazine, furosemide, antimicrobial drugs (especially sulfonamides, minocycline, vancomycin, β-lactam antibiotics, and isoniazid), some cardiovascular drugs (e.g., quinidine), and some antiretroviral drugs (e.g., nevirapine). *Exercise-induced hyperthermia* **(Chaps. 18 and 465)** is characterized by an elevated body temperature that is associated with moderate to strenuous exercise lasting from half an hour up to several hours without an increase in CRP level or ESR. Unlike patients with fever, these patients typically sweat during the temperature elevation. *Factitious fever* (fever artificially induced by the patient—for example, by IV injection of contaminated water) should be considered in all patients but is more common among young women in health-care professions. In *fraudulent fever*, the patient is normothermic but manipulates the thermometer. Simultaneous measurements at different body sites (rectum, ear, mouth) should rapidly identify this diagnosis. Another clue to fraudulent fever is dissociation between pulse rate and temperature.

Previous studies of FUO have shown that a cause is more likely to be found in elderly patients than in younger age groups. In many cases, FUO in the elderly results from an atypical manifestation of a common disease, among which giant cell arteritis and polymyalgia rheumatica are most frequently involved. Tuberculosis is the most common infectious disease associated with FUO in elderly patients, occurring much more often than in younger patients. As many of these diseases are treatable, it is well worth pursuing the cause of fever in elderly patients.

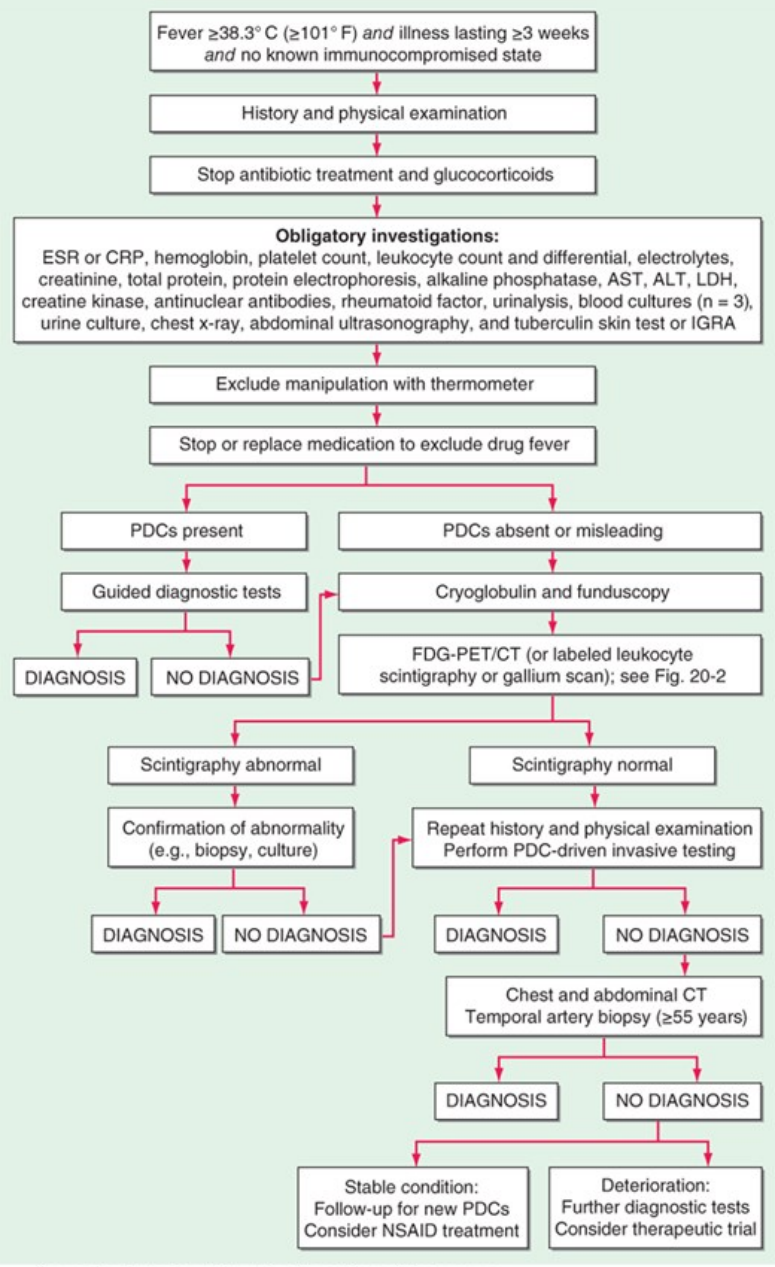
APPROACH TO THE PATIENT WITH FEVER OF UNKNOWN ORIGIN

First-Stage Diagnostic Tests

Figure 20-1 shows a structured approach to patients presenting with FUO. The most important step in the diagnostic workup is the search for potentially diagnostic clues (PDCs) through complete and repeated history-taking and physical examination and the obligatory investigations listed above and in the figure. *PDCs* are defined as all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis. Although PDCs are often misleading, only with their help can a concise list of probable diagnoses be made. The history should include information about the fever pattern (continuous or recurrent) and duration, previous medical history, present and recent drug use, family history, sexual history, country of origin, recent and remote travel, unusual environmental exposures associated with travel or hobbies, and animal contacts. A complete physical examination should be performed, with special attention to the eyes, lymph nodes, temporal arteries, liver, spleen, sites of previous surgery, entire skin surface, and mucous membranes. Before further diagnostic tests are initiated, antibiotic and glucocorticoid treatment, which can mask many diseases, should be stopped. For example, blood and other cultures are not reliable when samples are obtained during antibiotic treatment, and the size of enlarged lymph nodes usually decreases during glucocorticoid treatment, regardless of the cause of lymphadenopathy. Despite the high percentage of false-positive ultrasounds and the relatively low sensitivity of chest x-rays, the performance of these simple, low-cost diagnostic tests remains obligatory in all patients with FUO in order to separate cases that are caused by easily diagnosed diseases from those that are not. Abdominal ultrasound is preferred to abdominal CT as an obligatory test because of relatively low cost, lack of radiation burden, and absence of side effects.

FIGURE 20-1

Structured approach to patients with FUO. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography combined with low-dose CT; IGRA, interferon γ release assay; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drug; PDCs, potentially diagnostic clues (all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis).



Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e

Only rarely do biochemical tests (beyond the obligatory tests needed to classify a patient's fever as FUO) lead directly to a definitive diagnosis in the absence of PDCs. The diagnostic yield of immunologic serology other than that included in the obligatory tests is relatively low. These tests more often yield false-positive rather than true-positive results and are of little use without PDCs pointing to specific immunologic disorders. Given the absence of specific symptoms in many patients and the relatively low cost of the test, investigation of cryoglobulins appears to be a valuable screening test in patients with FUO.

Multiple blood samples should be cultured in the laboratory long enough to ensure ample growth time for any fastidious organisms, such as HACEK organisms. It is critical to inform the laboratory of the intent to test for unusual organisms. Specialized media should be used when the history suggests uncommon microorganisms, such as *Histoplasma* or *Legionella*. Performing more than three blood cultures or more than one urine culture is useless in patients with FUO in the absence of PDCs (e.g., a high level of clinical suspicion of endocarditis). Repeating blood or urine cultures is useful only when previously cultured samples were collected during antibiotic treatment or within 1 week after its discontinuation. FUO with headache should prompt microbiologic examination of cerebrospinal fluid (CSF) for organisms including herpes simplex virus (especially type 2), *Cryptococcus neoformans*, and *Mycobacterium tuberculosis*. In central nervous system tuberculosis, the CSF typically has elevated protein and lowered glucose

concentrations, with a mononuclear pleocytosis. CSF protein levels range from 100 to 500 mg/dL in most patients, the CSF glucose concentration is <45 mg/dL in 80% of cases, and the usual CSF cell count is between 100 and 500 cells/µL.

Microbiologic serology should not be included in the diagnostic workup of patients without PDCs for specific infections. A tuberculin skin test (TST) or interferon γ release assay (IGRA, QuantiFERON test) is included in the obligatory investigations, but it may yield false-negative results in patients with miliary tuberculosis, malnutrition, or immunosuppression. Although the IGRA is less influenced by prior vaccination with bacille Calmette-Guérin (BCG) or by infection with nontuberculous mycobacteria, its sensitivity is similar to that of the TST; a negative TST or IGRA therefore does not exclude a diagnosis of tuberculosis. Miliary tuberculosis is especially difficult to diagnose. Granulomatous disease in liver or bone marrow biopsy samples, for example, should always lead to a (re)consideration of this diagnosis. If miliary tuberculosis is suspected, liver biopsy for acid-fast smear, culture, and polymerase chain reaction probably still has the highest diagnostic yield; however, biopsies of bone marrow, lymph nodes, or other involved organs also can be considered.

The diagnostic yield of echocardiography, sinus radiography, radiologic or endoscopic evaluation of the gastrointestinal tract, and bronchoscopy is very low in the absence of PDCs. Therefore, these tests should not be used as screening procedures.

After identification of all PDCs retrieved from the history, physical examination, and obligatory tests, a limited list of the most probable diagnoses should be made. Since most investigations are helpful only for patients who have PDCs for the diagnoses sought, further diagnostic procedures should be limited to specific investigations aimed at confirming or excluding diseases on this list. In FUO, the diagnostic pointers are numerous and diverse but may be missed on initial examination, often being detected only by a very careful examination performed subsequently. In the absence of PDCs, the history and physical examination should therefore be repeated regularly. One of the first steps should be to rule out factitious or fraudulent fever, particularly in patients without signs of inflammation in laboratory tests. All medications, including nonprescription drugs and nutritional supplements, should be discontinued early in the evaluation to exclude drug fever. If fever persists beyond 72 h after discontinuation of the suspected drug, it is unlikely that this drug is the cause. In patients without PDCs or with only misleading PDCs, fundoscopy by an ophthalmologist may be useful in the early stage of the diagnostic workup to exclude retinal vasculitis. When the first-stage diagnostic tests do not lead to a diagnosis, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography combined with computed tomography (PET/CT) or, if the former is not available, radiolabeled leukocyte scintigraphy should be performed, especially when the ESR or the CRP level is elevated.

RECURRENT FEVER

In patients with recurrent fever, the diagnostic workup should consist of thorough history-taking, physical examination, and obligatory tests. The search for PDCs should be directed toward clues matching known recurrent syndromes **(Table 20-3)**. Patients should be asked to return during a febrile episode so that the history, physical examination, and laboratory tests can be repeated during a symptomatic phase. Further diagnostic tests, such as PET/CT or scintigraphic imaging (see below), should be performed only during a febrile episode or when inflammatory parameters are abnormal because abnormalities may be absent between episodes. In patients with recurrent fever lasting >2 years, it is very unlikely that the fever is caused by infection or malignancy. Further diagnostic tests in that direction should be considered only when PDCs for infections, vasculitis syndromes, or malignancy are present or when the patient's clinical condition is deteriorating.

TABLE 20-3

All Reported Causes of Recurrent Fever[a]

Infections	
Bacterial, nonspecific	Apical granuloma, diverticulitis, prostatitis, recurrent bacteremia caused by colonic neoplasia or persistent focal infection, recurrent cellulitis, recurrent cholangitis or cholecystitis, recurrent pneumonia, recurrent sinusitis, recurrent urinary tract infection
Bacterial, specific	Bartonellosis, brucellosis, chronic gonococcemia, chronic meningococcemia, louse-borne relapsing fever (*Borrelia recurrentis*), melioidosis (*Pseudomonas pseudomallei*), Q fever (*Coxiella burnetii*), salmonellosis, *Spirillum minor* infection, *Streptobacillus moniliformis* infection, syphilis, tick-borne relapsing fever (*Borrelia duttonii*), tularemia, Whipple's disease (*Tropheryma whipplei*), yersiniosis

Fungal	Coccidioidomycosis, histoplasmosis, paracoccidioidomycosis
Parasitic	Babesiosis, malaria, toxoplasmosis, trypanosomiasis, visceral leishmaniasis
Viral	Cytomegalovirus infection, Epstein-Barr virus infection, herpes simplex
Noninfectious Inflammatory Diseases	
Systemic rheumatic and autoimmune diseases	Ankylosing spondylitis, antiphospholipid syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behçet's disease, cryoglobulinemia, gout, polymyositis, pseudogout, reactive arthritis, relapsing polychondritis, systemic lupus erythematosus
Vasculitis	Churg-Strauss syndrome, giant cell vasculitis/polymyalgia rheumatica, hypersensitivity vasculitis, polyarteritis nodosa, urticarial vasculitis
Granulomatous diseases	Idiopathic granulomatous hepatitis, sarcoidosis
Autoinflammatory syndromes	Adult-onset Still's disease, Blau syndrome, CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature syndrome), CAPS[b] (cryopyrin-associated periodic syndrome), CRMO (chronic recurrent multifocal osteomyelitis), Crohn's disease, DIRA (deficiency of the interleukin 1 receptor antagonist), familial Mediterranean fever, hemophagocytic syndrome, hyper-IgD syndrome (HIDS, also known as mevalonate kinase deficiency), juvenile idiopathic arthritis, NLRC4-activating mutations, PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne), PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis), recurrent idiopathic pericarditis, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis), SAVI (stimulator of interferon genes [STING]–associated vasculopathy with onset in infancy), Schnitzler syndrome, TRAPS (tumor necrosis factor receptor–associated periodic syndrome)
Neoplasms	
	Angioimmunoblastic lymphoma, Castleman's disease, colon carcinoma, craniopharyngioma, Hodgkin's disease, malignant histiocytosis, mesothelioma, non-Hodgkin's lymphoma
Miscellaneous Causes	
	Adrenal insufficiency, aortic-enteral fistula, aseptic meningitis (Mollaret's syndrome), atrial myxoma, brewer's yeast ingestion, cholesterol emboli, cyclic neutropenia, drug fever, extrinsic allergic alveolitis, Fabry's disease, factitious disease, fraudulent fever, Gaucher disease, hypersensitivity pneumonitis, hypertriglyceridemia, hypothalamic hypopituitarism, inflammatory pseudotumor, metal fume fever, milk protein allergy, polymer fume fever, pulmonary embolism, sclerosing mesenteritis
Thermoregulatory Disorders	
Central	Hypothalamic dysfunction
Peripheral	Anhidrotic ectodermal dysplasia, exercise-induced hyperthermia, pheochromocytoma

[a]This table includes all causes of recurrent fever that have been described in the literature.

[b]CAPS includes chronic infantile neurologic cutaneous and articular syndrome (CINCA, also known as neonatal-onset multisystem inflammatory disease, or NOMID), familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome.

FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY

^{18}F-FDG PET/CT has become an established imaging procedure in FUO. FDG accumulates in tissues with a high rate of glycolysis, which occurs not only in malignant cells but also in activated leukocytes and thus permits the imaging of acute and chronic inflammatory processes. Compared with conventional scintigraphy (see below), FDG-PET/CT offers the advantages of higher resolution, greater sensitivity in chronic low-grade infections, and a high degree of accuracy in the central skeleton. Furthermore, vascular uptake of FDG is increased in patients with vasculitis **(Fig. 20-2)**. The mechanisms responsible for FDG uptake do not allow differentiation among infection, sterile inflammation, and malignancy. However, since all of these disorders are causes of FUO, FDG-PET/CT can be used to guide additional diagnostic tests (e.g., targeted biopsies) that may yield the final diagnosis. It is important to realize that physiologic uptake of FDG may obscure pathologic foci in the brain, heart, bowel, kidneys, and bladder. FDG uptake in the heart, which obscures endocarditis, may be prevented by consumption of a low-carbohydrate diet before the PET investigation. In patients with fever, bone marrow uptake is frequently increased in a nonspecific way due to cytokine activation, which upregulates glucose transporters in bone marrow cells.

FIGURE 20-2

FDG-PET/CT in a patient with FUO. This 72-year-old woman presented with a low-grade fever and severe fatigue of almost 3 months' duration. An extensive history was taken, but the patient had no specific complaints and had not traveled recently. Her previous history was unremarkable, and she did not use any drugs. Physical examination, including palpation of the temporal arteries, yielded completely normal results. Laboratory examination showed normocytic anemia, a C-reactive protein level of 43 mg/L, an erythrocyte sedimentation rate of 87 mm/h, and mild hypoalbuminemia. Results of the other obligatory tests were all normal. Since there were no potentially diagnostic clues, FDG-PET/CT was performed. This test showed increased FDG uptake in all major arteries (carotid, jugular, and subclavian arteries; thoracic and abdominal aorta; iliac, femoral, and popliteal arteries) and in the soft tissue around the shoulders, hips, and knees—findings compatible with large-vessel vasculitis and polymyalgia rheumatica. Within 1 week after the initiation of treatment with prednisone (60 mg once daily), the patient completely recovered. After 1 month, the prednisone dose was slowly tapered. *(Source: JL Jameson, AS Fauci, DL Kasper, SL Hauser, DL Longo, J Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition Copyright © McGraw Hill Education. All rights reserved.)*

In recent years, many cohort studies and several meta-analyses have focused on the diagnostic yield of PET and PET/CT in FUO. These studies are highly variable in terms of the selection of patients, the follow-up, and the selection of a gold-standard reference. Indirect comparisons of test performance suggested that FDG-PET/CT outperformed stand-alone FDG-PET, gallium scintigraphy, and leukocyte scintigraphy. Similarly, indirect comparisons of diagnostic yield suggested that FDG-PET/CT was more likely than alternative tests to correctly identify the cause of FUO. Meta-analyses report a high diagnostic yield for PET and PET/CT in the workup of FUO patients, with pooled sensitivity and specificity figures of ~85% and ~50%, respectively, and a total diagnostic yield of ~50% for PET/CT and ~40% for PET.

As many patients with FUO present with periodic fever, correct timing of PET/CT increases its diagnostic value. Few studies on the use of biomarkers such as elevated CRP or ESR for a contributory outcome of PET/CT have been performed. When both CRP and ESR are normal at the time of FDG-PET/CT, outcome may only be contributory when a patient does have fever at the time of the scan.

Although PET/CT and other scintigraphic techniques do not directly provide a definitive diagnosis (with the exception of some patients with, for instance, large vessel vasculitis), they often identify the anatomic location of a particular ongoing metabolic process. With the help of other techniques such as biopsy and culture, a timely diagnosis and treatment can be facilitated. Pathologic FDG uptake is quickly eradicated by treatment with glucocorticoids in many diseases, including vasculitis and lymphoma; therefore, glucocorticoid use should be stopped or postponed until after FDG-PET/CT is performed.

FDG-PET/CT is a relatively expensive procedure whose availability is still limited compared with that of CT and conventional scintigraphy. Nevertheless, FDG-PET/CT can be cost-effective in the FUO diagnostic workup if used at an early stage, helping to establish an early diagnosis, reducing days of hospitalization for diagnostic purposes, and obviating unnecessary and unhelpful tests. When FDG-PET/CT has been made under the right conditions (i.e., when elevated CRP or ESR or fever were present during the scan) but has not contributed to the final diagnosis, repeating PET/CT is probably of little value, unless new signs or symptoms appear.

CONVENTIONAL SCINTIGRAPHIC IMAGING OTHER THAN PET/CT

Conventional scintigraphic methods used in clinical practice are ^{67}Ga-citrate scintigraphy and ^{111}In- or ^{99m}Tc-labeled leukocyte scintigraphy. Sensitivity and specificity of conventional scintigraphic studies are lower than for PET/CT: the diagnostic yield of gallium scintigraphy ranges from 21% to 54%, and on average the location of a source of fever can correctly be localized in approximately one-third of patients. The diagnostic value of leukocyte scintigraphy ranges from 8% to 31%, and overall the cause of FUO can correctly be identified in one-fifth of patients. When PET/CT is not available, these techniques are the only alternative.

Later-Stage Diagnostic Tests

In some cases, more invasive tests are appropriate. Abnormalities found with imaging often need to be confirmed by pathology and/or culture of biopsy specimens. If lymphadenopathy is found, lymph node biopsy is necessary, even when the affected lymph nodes are hard to reach or when previous biopsies were inconclusive. In the case of skin lesions, skin biopsy should be undertaken.

If no diagnosis is reached despite PET/CT and PDC-driven histologic investigations or culture, second-stage screening diagnostic tests should be considered (Fig. 20-1). In three studies, the diagnostic yield of screening chest and abdominal CT in patients with FUO was ~20%. The specificity of chest CT was ~80%, but that of abdominal CT varied between 63% and 80%. Despite the relatively limited specificity of abdominal CT and the probably limited additional value of chest CT after normal FDG-PET/CT, chest and abdominal CT may be used as screening procedures at a later stage of the diagnostic protocol because of their noninvasive nature and high sensitivity. Bone marrow aspiration is seldom useful in the absence of PDCs for bone marrow disorders. With addition of FDG-PET/CT, which is highly sensitive in detecting lymphoma, carcinoma, and osteomyelitis, the value of bone marrow biopsy as a screening procedure is probably further reduced. Several studies have shown a high prevalence of giant cell arteritis among patients with FUO, with rates up to 17% among elderly patients. Giant cell arteritis often involves large arteries and in most cases can be diagnosed by FDG-PET/CT. However, temporal artery biopsy is still recommended for patients ≥55 years of age in a later stage of the diagnostic protocol: FDG-PET/CT will not be useful in vasculitis limited to the temporal arteries because of the small diameter of these vessels and the high levels of FDG uptake in the brain. In the past, liver biopsies were often performed as a screening procedure in patients with FUO. In each of two studies, liver biopsy as part of the later stage of a screening diagnostic protocol was helpful in only one patient. Moreover, abnormal liver tests are not predictive of a diagnostic liver biopsy in FUO. Liver biopsy is an invasive procedure that carries the possibility of complications and even death. Therefore, it should not be used for screening purposes in patients with FUO except in those with PDCs for liver disease or miliary tuberculosis.

In patients with unexplained fever after all of the above procedures, the last steps in the diagnostic workup—with only a marginal diagnostic yield—come at an extraordinarily high cost in terms of both expense and discomfort for the patient. Repetition of a thorough history-taking and physical examination and review of laboratory results and imaging studies (including those from other hospitals) are recommended. Diagnostic delay often results from a failure to recognize PDCs in the available information. In these patients with persisting FUO, waiting for new PDCs to appear probably is better than ordering more screening investigations. Only when a patient's condition deteriorates without providing new PDCs should a further diagnostic workup be performed.

Second Opinion in an Expert Center

When despite the workup described above no explanation for FUO is found, second opinion in an expert center on FUO should be considered. The single study on the value of second opinion in FUO reported that in 57.3% of patients with unexplained FUO, a diagnosis could be found in an expert center. Additionally, of all patients who remained without a diagnosis even after second opinion, 10.9% became fever-free upon empirical treatment, adding up to a beneficial outcome in 68.2% of patients.

TREATMENT OF FEVER OF UNKNOWN ORIGIN

Empirical therapeutic trials with antibiotics, glucocorticoids, or antituberculous agents should be avoided in FUO except when a patient's condition is rapidly deteriorating after the aforementioned diagnostic tests have failed to provide a definite diagnosis.

Antibiotics and Antituberculous Therapy

Antibiotic or antituberculous therapy may irrevocably diminish the ability to culture fastidious bacteria or mycobacteria. However, hemodynamic instability or neutropenia is a good indication for empirical antibiotic therapy. If the TST or IGRA is positive or if granulomatous disease is present with anergy and sarcoidosis seems unlikely, a trial of therapy for tuberculosis should be started. Especially in miliary tuberculosis, it may be very difficult to obtain a rapid diagnosis. If the fever does not respond after 6 weeks of empirical antituberculous treatment, another diagnosis should be considered.

Colchicine, Nonsteroidal Anti-Inflammatory Drugs, and Glucocorticoids

Colchicine is highly effective in preventing attacks of familial Mediterranean fever (FMF) but is not always effective once an attack is well under way. When FMF is suspected, the response to colchicine is not a completely reliable diagnostic tool in the acute phase, but with colchicine treatment most patients show remarkable improvements in the frequency and severity of subsequent febrile episodes within weeks to months. Therefore, colchicine may be tried in patients with features compatible with FMF, especially when these patients originate from a high-prevalence region.

If the fever persists and the source remains elusive after completion of the later-stage investigations, supportive treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful. The response of adult-onset Still's disease to NSAIDs is dramatic in some cases.

The effects of glucocorticoids on giant cell arteritis and polymyalgia rheumatica are equally impressive. Early empirical trials with glucocorticoids, however, decrease the chances of reaching a diagnosis for which more specific and sometimes life-saving treatment might be more appropriate, such as malignant lymphoma. The ability of NSAIDs and glucocorticoids to mask fever while permitting the spread of infection or lymphoma dictates that their use should be avoided unless infectious diseases and malignant lymphoma have been largely ruled out and inflammatory disease is probable and is likely to be debilitating or threatening.

Interleukin 1 Inhibition

Interleukin (IL) 1 is a key cytokine in local and systemic inflammation and the febrile response. The availability of specific IL-1-targeting agents has revealed a pathologic role of IL-1-mediated inflammation in a growing list of diseases. Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra), blocks the activity of both IL-1α and IL-1β. Anakinra is extremely effective in the treatment of many autoinflammatory syndromes, such as FMF, cryopyrin-associated periodic syndrome, tumor necrosis factor receptor–associated periodic syndrome, mevalonate kinase deficiency (hyper IgD syndrome), Schnitzler syndrome, and adult onset Still's disease. There are many other chronic inflammatory disorders in which anti-IL-1 therapy is highly effective. A therapeutic trial with anakinra can be considered in patients whose FUO has not been diagnosed after later-stage diagnostic tests. Although most chronic inflammatory conditions without a known basis can be controlled with glucocorticoids, monotherapy with IL-1 blockade can provide improved control without the metabolic, immunologic, and gastrointestinal side effects of glucocorticoid administration.

PROGNOSIS

In patients in whom FUO remains unexplained, prognosis is favorable. Two large studies on mortality in these patients have been performed. The first study included 436 patients of whom 168 remained without a diagnosis. Of these, 4 (2.4%) died during follow-up. All 4 patients died during the index admission, and in 2 of them a diagnosis was made upon autopsy (1 had intravascular lymphoma and 1 had bilateral pneumonia). The second study included 131 patients with unexplained FUO. Of these patients, 9 (6.9%) died during a median follow-up of 5 years. In 6 of these patients the cause of

death was known, and in 5 of them death was considered unrelated to the febrile disease. Overall, FUO-related mortality rates have continuously declined over recent decades. The majority of fevers are caused by treatable diseases, and the risk of death related to FUO is, of course, dependent on the underlying disease.

FURTHER READING

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