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example, an eschar may suggest the diagnosis of scrub typhus or rickett sialpox (Fig. A1-33A) (Chap. 192) in the appropriate setting. In other illnesses (e.g., anthrax) (Fig. A1-52) (Chap. S4), an ulcer or eschar may be the only skin manifestation. ■ ■FURTHER READING Cherry JD: Cutaneous manifestations of systemic infections, in Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 8th ed. JD Cherry et al (eds). Philadelphia, Elsevier, 2019, pp 539–559. Juliano JJ et al: The acutely ill patient with fever and rash, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, vol 1, 10th ed. MJ Blaser et al (eds). Philadelphia, Elsevier, 2025. Kang S et al (eds): Fitzpatrick's Dermatology, 9th ed. New York, McGraw-Hill, 2019. Saavedra AP et al: Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 9th ed. New York, McGraw Hill, 2023. Catharina M. Mulders-Manders,

Chantal P. Rovers

Fever of Unknown Origin ■ ■DEFINITION Clinicians commonly refer to any febrile illness without an initially obvious etiology as fever of unknown origin (FUO). Most febrile ill nesses either resolve before a diagnosis can be made or develop distin guishing characteristics that lead to a diagnosis. The term FUO should be reserved for prolonged febrile illnesses without an established etiol ogy 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 at least 3 weeks' duration with fever of ≥38.3°C (≥101°F) on two occasions and an uncertain diagnosis despite 1 week of inpatient evaluation. Since then, several modifications of the definition have been proposed to better reflect outpatient-based health care and to exclude immunocompromised patients, who require a different and more aggressive approach. To reduce heterogeneity between cohorts, inclusion of qualitative criteria of minimal diagnostic testing are neces sary. Accordingly, FUO is now defined as:

1. Fever ≥38.3°C (≥101°F) on at least two occasions
2. Illness duration of at least 3 weeks
3. No known immunocompromised state TABLE 22-1 Etiology of FUO: Pooled Results of Large Studies Published in the Past 20 Years (2003–2023) NO. OF COHORTS (INCLUSION PERIOD) NO. OF PATIENTS INFECTIONS, MEDIAN % (RANGE) GEOGRAPHIC AREA Western Europe

(1995–2020)

15.5 (4–36) Other European and Turkey

(1984–2019)

(26–74) Middle East

(2009–2010)a

(42–79) Asia

(1994–2021)a

(3–58) Note: No studies from the Americas, Africa, or Oceania have been reported. Studies aimed at diagnostic methods were excluded. aSome studies did not report an inclusion period. For references, see supplementary material at accessmedicine.com/harrisons.

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 electropho resis; urinalysis; blood cultures (n = 3); urine culture; chest x-ray; abdominal ultrasonography; and tuberculin skin test (TST) or inter feron γ release assay (IGRA) Fever of Unknown Origin CHAPTER 22 Closely related to FUO is inflammation of unknown origin (IUO), which has the same definition as FUO, except for the body tempera ture criterion: IUO is defined as the presence of elevated inflamma tory 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 historytaking, physical examination, and the obligatory tests listed above. It has been shown in multiple cohorts that the causes for IUO and FUO are the same and that their workup should be identical. Therefore, for convenience, the term FUO will refer to both FUO and IUO within the remainder of this chapter. ■ ■ETIOLOGY AND EPIDEMIOLOGY The prevalence of FUO is largely unknown and will likely vary between different geographic regions and different health care settings. In the 1990s, Japan reported a prevalence of 2.9% in admitted patients, and a recent Danish registry study reported 6220 patients in a 10-year time frame. Table 22-1 summarizes the findings of large studies on FUO conducted over the past 20 years. Since the 1960s, the range of FUO etiologies has evolved as a result of changes in the definition, local disease epidemiology, the wide spread use of antibiotics, and especially the availability of new diag nostic 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 or autoinflammatory diseases, were unknown six decades ago. Data on the outcome of FUO are difficult to compare between studies because of variability in patient selection and variability in workup between cohorts. Study

outcome strongly depends on study design and the origin of the cohort. The chance of a final diagnosis is higher when (older) time-based criteria are used versus when (newer) criteria including a standard basic workup are used for patient selec tion. The chance of remaining without a final diagnosis is two to five times higher in patients from Europe compared to patients from Asia. NONINFECTIOUS INFLAMMATORY DISEASES, MEDIAN % (RANGE) NO DIAGNOSIS, MEDIAN % (RANGE) MALIGNANCY, MEDIAN % (RANGE) MISCELLANEOUS, MEDIAN % (RANGE)

(17–33)

(3–30) 7.5 (0–16) 39.5 (26–54)

(12–38)

(4–19)

(2–18)

(0–35)

(7–17)

(1–30)

(0–12)

(2–12)

(7–57)

(6–23) 6.5 (0–15)

(0–81)

Roughly comparable to 60 years ago, infections remain the most common cause of FUO in non-Western cohorts. Compared to Europe, the risk of having an infection is over four times higher in patients from Southern Asia and three times higher in far East Asia. 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 on FUO 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. Up to 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 inflammation may precede more typical manifestations or laboratory evidence of these diseases by months. Moreover, NIIDs may only be diagnosed after prolonged observation and exclusion of other diseases, and an increasing num ber of genetic inflammatory syndromes have been described in more recent years.

PART 2 Cardinal Manifestations and Presentation of Diseases Especially in Western cohorts, where the proportion of undiagnosed patients can be up to >50%, the proportion of patients remaining without a final diagnosis is much higher than 60 years ago despite technical advantages. This is called “the FUO paradox” and 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 diagnostic techniques such as CT, MRI, and positron emission tomography (PET)/CT, are now widely 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. No clinical parameters or tools that can help identify patients with a high risk of remaining undiagnosed have been identified. Recurrent inflammation (defined as repeated episodes of fever or inflammation interspersed with fever-free intervals of at least 2 weeks and apparent remission of the underlying disease) reduces the chance of finding a final explanation and is associated with a lower, but not zero, preva lence of infections. A symptom duration of >12 months is significantly associated with a lower chance of finding a final explanation, and infec tions and malignancy are less common, but still a possibility, in patients with such extensive symptom duration. It is important to note that even in patients with symptom duration >3 months, more common infections such as tuberculosis, spondylodiscitis, and endocarditis have been described and that lymphoma has been reported in patients with symptom duration >12 months. Normal PET/CT has also been associ ated with a lower chance of a final diagnosis. Artificial intelligence, using computer models to predict the final diagnosis in patients with FUO, may be able to shorten diagnostic delay and may guide specific diagnostic testing, but only limited data are available. Its exact value on a larger scale, especially in different geographic regions, is difficult to estimate at this moment. ■ ■DIFFERENTIAL DIAGNOSIS The differential diagnosis for FUO is extensive. It is important to note that patients with FUO most often suffer from an atypical presentation of a more common disease, rather than from a rare disease. Unsurpris ingly, the distribution of causes of FUO is influenced by local epide miology. Table 22-2 presents an overview of possible causes of FUO. Endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmo nary tuberculosis are the more common infectious disease diagnoses. Q fever (Coxiella burnetii) and Whipple’s disease (Tropheryma whipplei infection) are quite rare but should always be kept in mind as causes of FUO since the presenting symptoms can be nonspecific. Serologic test ing for Q fever, which results from exposure to animals or animal prod ucts, 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 T. whipplei should be performed on stool and blood early in the diagnostic process. Travel to or (former) residence in tropical countries or the American Southwest should lead to consideration of endemic 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. 133) may be due to difficult-to-culture bacteria such as nutritionally vari ant bacteria, HACEK organisms (including Haemophilus parainflu enzae, H. paraphrophilus, Aggregatibacter actinomycetemcomitans, A. aphrophilus, A. paraphrophilus, Cardiobacterium hominis, C. valvarum, Eikenella corrodens, and Kingella kingae), 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 sys temic lupus erythematosus and antiphospholipid syndrome. The use of next-generation sequencing for rapid detection of infecting microbes may be valuable in patients with FUO, but its exact value and exact application are yet to be determined. Of the NIIDs, adult-onset Still's disease, large-vessel vasculitis, polymyalgia rheumatica, systemic lupus erythematosus (SLE), and sarcoidosis are rather common diagnoses in patients with FUO. Autoinflammatory syndromes are rare (with the exception of familial Mediterranean fever in specific geographic regions), and most can only be diagnosed on clinical criteria. Schnitzler's syndrome, which can present at any age, can often be diagnosed easily in a patient with FUO who presents with urticaria, bone pain, and monoclonal gammopa thy. A new autoinflammatory syndrome called vacuoles, E1 enzyme, X-linked autoinflammatory syndrome (VEXAS) has been described in

> 300 patients since 2020. VEXAS is an adult-onset multisystem auto inflammatory syndrome with predominance in middle-aged to elderly males and is characterized, among others, by recurrent inflammation, skin lesions, chondritis, lung disease, venous thrombosis, arthritis, and myelodysplastic syndrome. The presence of vacuoles in myeloid precursors in bone marrow biopsy is very suspicious for VEXAS in a patient with inflammatory symptoms. The disease is caused by somatic mosaicism for pathogenic variants in UBA1. Although most malignancies 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 or benign 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; now more generally referred to as drug-induced hypersensitivity syndrome [DIHS]; 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, and antimicrobial drugs (espe cially sulfonamides, minocycline, vancomycin, β-lactam antibiotics, and isoniazid). Benign hyperthermia or exercise-induced hyperthermia (Chaps. 20 and 478) is characterized by an elevated body tempera ture without an increase in CRP or ESR or other signs of inflamma tion; these may be postinfectious in origin. Infectious triggers for benign hyperthermia are possibly the same as for chronic fatigue syndrome, such as Epstein-Barr virus, Q-fever, and COVID-19. Factitious fever (fever artificially induced by the patient—for exam ple, by IV injection of contaminated water) should be considered in all patients, especially those with easy access to medical equipment. 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.

Fever of Unknown Origin CHAPTER 22 TABLE 22-2 Reported Causes of Fever of Unknown Origin (FUO)a Infections Bacterial, nonspecific Abdominal abscess, adnexitis, aortitis, apical granuloma, appendicitis, bacterial translocation, bronchiectasis, cholangitis, cholecystitis, diverticulitis, endocarditis, endometritis, epididymitis, epidural abscess, infected joint prosthesis, infected vascular catheter, infected vascular prosthesis, infectious arthritis, infective myonecrosis, intracranial abscess, liver abscess, lung abscess, malakoplakia, mastitis, mastoiditis, mediastinitis, muscle abscess, mycotic aneurysm, osteomyelitis, pelvic inflammatory disease, prostatitis, pyelonephritis, pylephlebitis, pyomyoma, renal abscess, septic arthritis, septic phlebitis, sinusitis, spondylodiscitis, xanthogranulomatous urinary tract infection Bacterial, specific Actinomycosis, Bacteroides, bartonellosis, brucellosis, Bacillus Calmette-Guérin infection, Burkholderia spp., Campylobacter infection, Chlamydia pneumoniae infection, chronic meningococcemia, ehrlichiosis, enterococci, Escherichia coli, Gemella infection, gonococcus, Klebsiella spp., Lactobacillus, legionellosis, leptospirosis, listeriosis, louse-borne relapsing fever (Borrelia recurrentis), Lyme disease (Borrelia burgdorferi), melioidosis (Burkholderia pseudomallei), Mycoplasma infection, nocardiosis, nontuberculous mycobacteria, Prevotella infection, Pseudomonas spp., psittacosis, Q fever (Coxiella burnetii), rickettsiosis, Rhodococcus spp., Salmonella spp., Spirillum minor infection, Sphingobacterium infection, Staphylococcus aureus, Streptobacillus moniliformis infection, syphilis, tick-borne relapsing fever (Borrelia duttonii, Borrelia hermsi), tuberculosis, tularemia, typhoid fever and other salmonelloses, Whipple disease (Tropheryma whipplei), yersiniosis Fungal Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, Malassezia furfur infection, mucormycosis, paracoccidioidomycosis, Penicillium spp., Pneumocystis jirovecii pneumonia, sporotrichosis, Talaromyces infection Parasitic Amebiasis, babesiosis, echinococcosis, fascioliasis, malaria, schistosomiasis, strongyloidiasis, toxocariasis, toxoplasmosis, trichinellosis, trypanosomiasis, visceral leishmaniasis Viral Colorado tick fever, coxsackievirus infection, cytomegalovirus infection, chikungunya, 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, neuromyelitis optica, polymyositis, pseudogout, reactive arthritis, psoriatic arthritis, relapsing polychondritis, rheumatic fever, rheumatoid arthritis, Sjögren’s syndrome, systemic lupus erythematosus, systemic sclerosis, Vogt-Koyanagi-Harada syndrome Vasculitis Allergic vasculitis, antineutrophil cytoplastic antibody (ANCA) vasculitis, Cogan’s syndrome, eosinophilic granulomatosis with polyangiitis, giant cell vasculitis/polymyalgia rheumatica, granulomatosis with polyangiitis, hypersensitivity vasculitis, IgA vasculitis, Kawasaki disease, polyarteritis nodosa, Takayasu arteritis, urticarial vasculitis Granulomatous diseases Idiopathic granulomatous hepatitis, sarcoidosis Autoinflammatory syndromes Blau syndrome, CAPSb (cryopyrin-associated periodic syndromes), Crohn’s disease, DIRA (deficiency of the interleukin 1 receptor antagonist), deficiency of adenosine deaminase 2 (DADA2), familial Mediterranean fever, hyper-IgD syndrome (HIDS, due to mevalonate kinase deficiency), juvenile idiopathic arthritis, macrophage activation syndrome, NLRP12-related disease, 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's syndrome, Still's disease, TRAPS (tumor necrosis factor receptor– associated periodic syndrome), VEXAS (vacuoles, E1 enzyme, X-linked autoinflammatory syndrome) Neoplasms Hematologic malignancies Amyloidosis, angioimmunoblastic lymphoma, Castleman's disease, hemophagocytic syndrome (hemophagocytic lymphohistiocytosis), 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 common 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, tumoral calcinosis Miscellaneous Causes ADEM (acute disseminated encephalomyelitis), adrenal insufficiency, alcoholic steatohepatitis, allergic purpura, aneurysms, anal fistula, antiNMDA encephalitis, antisynthetase syndrome, anomalous thoracic duct, aortic dissection, aortic-enteral fistula, aseptic meningitis (Mollaret's syndrome), atrial myxoma, brewer's yeast ingestion, calcium pyrophosphate deposition, Caroli's disease, cholesterol emboli, cirrhosis, complex partial status epilepticus, crowned dense syndrome, cyclic neutropenia, cryptogenic organizing pneumonia, drug fever, Erdheim-Chester disease, extrinsic allergic alveolitis, Fabry's disease, factitious disease, fire-eater's lung, fraudulent fever, Dressler's syndrome, ganglioneuroma, extrinsic allergic alveolitis, Gaucher's disease, hemolytic uremic syndrome, Hamman-Rich syndrome (acute interstitial pneumonia), Hashimoto's encephalopathy, hematoma, heparin-induced thrombocytopenia, histiocytic necrotizing lymphadenitis, hypersensitivity pneumonitis, hypertriglyceridemia, hypogammaglobulinemia/subclass deficiency, hypothalamic hypopituitarism, idiopathic inflammatory myopathy, idiopathic normal-pressure hydrocephalus, IgG4 disease, inflammatory pseudotumor, interstitial nephritis, Kikuchi's disease, limbic encephalitis, linear IgA dermatosis, mesenteric fibromatosis, metal fume fever, microaspiration, milk protein allergy, Mollaret's meningitis, myotonic dystrophy, nonbacterial osteitis, obstructive suppurative pancreatic ductitis, organic dust toxic syndrome, panniculitis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes), obstructive sleep apnea syndrome, organizing pneumonia, polymer fume fever, post–cardiac injury syndrome, primary biliary cirrhosis, primary hyperparathyroidism, pseudomembranous colitis, pulmonary embolism, pulmonary nodular lymphoid hyperplasia, pyoderma gangrenosum, recurrent large bowel ischemia, retroperitoneal fibrosis, Rosai-Dorfman disease, sclerosing mesenteritis, silicone embolization, subacute thyroiditis (de Quervain's), Sweet's syndrome (acute febrile neutrophilic dermatosis), thrombosis, TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly) tubulointerstitial nephritis and uveitis syndrome (TINU), ulcerative colitis, XIAP deficiency (X-linked inhibitor of apoptosis deficiency) Thermoregulatory Disorders Central Brain tumor, cerebrovascular accident, encephalitis, hypothalamic dysfunction Peripheral Anhidrotic ectodermal dysplasia, benign hyperthermia, exercise-induced hyperthermia, heat stroke, hyperthyroidism, paroxysmal sympathetic hyperactivity, pheochromocytoma aThis table includes causes of FUO that have been described in the literature. bCAPS 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.

Fever ≥38.3°C (101°F) AND illness ≥3 weeks AND no known immunocompromised state History and physical examination Stop antibiotic treatment and corticosteroids Obligatory investigations: CRP or ESR, hemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, AST, ALT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n = 3), urine culture, chest X-ray, abdominal ultrasonography, and tuberculin skin test or IGRA PART 2 Cardinal Manifestations and Presentation of Diseases Exclude manipulation with thermometer Exclude drug fever (stop or replace medication) PDCs present PDCs absent or misleading Guided diagnostic tests Diagnosis No diagnosis 18F-FDG-PET/CT* Abnormal Normal Confirmation of abnormality (e.g., biopsy, culture) Repeat history and physical examination PDC driven invasive testing Diagnosis No diagnosis Diagnosis No diagnosis Follow up for new PDCs Consider NSAID FIGURE 22-1 Structured approach to patients with FUO. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; 18F-FDG-PET/CT, 18F-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). *If not available, gallium scintigraphy or labeled leukocyte scintigraphy is an acceptable alternative. APPROACH TO THE PATIENT A Structured Diagnostic Approach Figure 22-1 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 com plete 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

Cryoglobulin and fundoscopy Stable condition Deterioration Further diagnostic tests Consider therapeutic trial medical history, present and recent drug use, family history, sexual history, country of origin, recent and remote travel, environmental exposures associated with travel or hobbies, and animal contacts. A complete physical examination should be performed, with spe cial 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, sterile blood and other cultures are not completely 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 and conventional chest radiography have been preferred to thoracic and abdominal CT as an obligatory test because of their relatively low cost, lower radiation burden, and absence of side effects. 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 inves tigations 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 subse quent careful examinations. In the absence of PDCs, the history and physical examination should be repeated regularly. In patients with recurrent inflammation, the diagnostic workup is the same as for patients with continuous inflammation. Patients should be asked to return during a febrile episode so that the history, physical exami nation, and laboratory tests can be repeated during a symptomatic phase. Further diagnostic tests should be performed only during an inflammatory episode because abnormalities may be absent between episodes. One of the first steps should be to rule out benign hyperthermia or factitious or fraudulent fever, particularly in patients without signs of inflammation in laboratory tests. All medications, includ ing 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. 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 immuno logic serologies other than those 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 disorders. Given the absence of specific symptoms in many patients and the relatively low cost of the test, investigation of cryo globulins 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 time for any fastidious organisms, such as those of the HACEK group. 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 dur ing 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 C. gattii, and Mycobacterium tuberculosis. Microbiologic serology should not be included in the diagnostic workup of patients without PDCs for specific infections. A tuber culin skin test (TST) or interferon γ (IFNγ) release assay (IGRA) is included in the obligatory investigations, but it may yield indetermi nate results in patients with miliary tuberculosis, with malnutrition, receiving immunosuppression, or with anti-IFNγ autoantibodies. Although the IGRA is less influenced by prior vaccination with bacille Calmette-Guérin (BCG) or by infection with most nontu berculous mycobacteria, its sensitivity is similar to that of the TST; a negative TST or IGRA does not exclude a diagnosis of tuberculosis. Miliary tuberculosis is especially difficult to diagnose. Granuloma tous 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. Mycobacterial polymerase chain reaction (PCR) testing together with cultures may shorten the time to diagnosis compared to mycobacterial cultures alone. The diagnostic yield of echocardiography, sinus radiography, radiologic or endoscopic evaluation of the gastrointestinal tract, bone marrow biopsy, liver biopsy, and bronchoscopy is very low in the absence of PDCs. Fever of Unknown Origin CHAPTER 22 In patients without PDCs or with only misleading PDCs,

fundos copy by an ophthalmologist may be useful early in the diagnostic workup to exclude retinal vasculitis. Several studies have shown a high prevalence of giant cell arte ritis 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 18F-fluordeoxyglucose (18F-FDG) positron emission tomography (PET) with combined CT. However, temporal artery biopsy is still recommended for patients ≥55 years. 18F-FDG-PET/CT may be confounded 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. When PDC-guided diagnostic tests do not lead to a diagnosis, 18F-FDG-PET/CT should be performed, preferably at a time point with elevated ESR or CRP to increase the chance of positive find ings. This is especially important in patients with episodic FUO. 18F-FLUORDEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY 18F-FDG-PET 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 leu kocytes and thus permits the imaging of acute and chronic inflam matory processes. Compared with conventional scintigraphy (see below), 18F-FDG-PET/CT offers the advantages of higher resolu tion, 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. 22-2). The mechanisms responsible for FDG uptake do not allow differ entiation among infection, sterile inflammation, and malignancy, but because all of these can cause FUO, this is an overall advantage. It is important to realize that physiologic uptake or concentration of FDG may obscure pathologic foci in the brain, heart, bowel, kid neys, and bladder. FDG uptake in the heart, which obscures endo carditis, may be prevented by consumption of a low-carbohydrate diet before the PET investigation. FDG uptake in the brain may obscure local temporal large vessel vasculitis. 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. In recent years, many cohort studies and several meta-analyses have focused on the diagnostic yield of 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 18F-FDG-PET/ CT outperformed gallium scintigraphy and leukocyte scintigraphy. Similarly, indirect comparisons of diagnostic yields suggested that 18F-FDG-PET/CT was more likely than alternative tests to correctly identify the cause of FUO. Meta-analyses report a high diagnostic yield of PET/CT in the workup of FUO patients, with total diag nostic yield (i.e., the proportion of scans helpful in finding the final explanation for the inflammation) of ~50% for PET/CT. As many patients with FUO present with periodic fever, the correct timing of PET/CT increases its diagnostic value. Few studies on the use of biomarkers, such as elevated CRP or ESR, as contributors to outcome of PET/CT have been performed. When both CRP and ESR are normal at the time of 18F-FDG-PET/CT, the outcome may only be contributory if a patient does have fever at the time of the scan.

 FIGURE 22-2 18F-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. 18F-FDG-PET/CT 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. 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 iden tify the anatomic location of a particular ongoing metabolic pro cess. 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 18F-FDG-PET/CT is performed. 18F-FDG-PET/CT is a relatively expensive procedure whose avail ability is still limited in some regions. Nevertheless, 18F-FDG-PET/CT can be cost-effective in the FUO diagnostic workup if used early, helping to establish an early diagnosis, reducing days of hospital ization for diagnostic purposes, and obviating unnecessary and unhelpful tests. When 18F-FDG-PET/CT has been made under the right conditions (i.e., during active inflammation) but has not contributed to the final diagnosis, repeating PET/CT is probably of little value, unless new signs or symptoms appear. ALTERNATIVES TO POSITRON EMISSION TOMOGRAPHY/ COMPUTED TOMOGRAPHY When PET/CT is unavailable, other whole-body imaging modali ties should be considered. Compared to CT, scintigraphy provides the location of active inflammation. Conventional scintigraphic methods in clinical practice are 67Ga-citrate scintigraphy and 111In- or 99mTc-labeled leukocyte scintigraphy. The diagnostic yields of these 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. Recently, one study of full-body MRI as an alternative for PET/CT reported a diagnostic yield comparable to PET/CT. Further studies are needed to confirm this finding.

LATER-STAGE DIAGNOSTIC TESTS Later-stage diagnostic testing should always be PDC driven and may come from repeated history-taking, physical examination, or PET/CT. Biopsies for pathology and/or microbiology evaluation will often be necessary. Diagnostic delay frequently results from a failure to recognize PDCs in the available information. When all PDCs have been thoroughly evaluated but no final explanation has been found, 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 further diagnostic workup be performed. SECOND OPINION IN AN EXPERT CENTER When no explanation for FUO is found despite the workup described above, a second opinion from an FUO expert center should be considered. The single study on the value of second opinion in FUO reported that in over half of patients with unexplained FUO, a diagnosis could be found in an expert center. Additionally, of all patients who remained without a diagnosis after second opinion, 1 in 10 became fever-free upon empirical treatment, adding up to a ben eficial outcome in a little under 70% of patients. One of the reasons for the higher diagnostic rate in expert centers is the fact that FUO is often an atypical presentation of a common disease, making pattern recognition informed by high exposure an important diagnostic tool. TREATMENT Fever of Unknown Origin Rational treatment is based on the final diagnosis. In FUO patients remaining with unexplained FUO, the large majority may sponta neously become symptom-free. Empirical therapeutic trials should be avoided, except in cases in which a patient’s condition is

rapidly deteriorating. Drugs that are commonly used for therapeutic tri als are antibiotics, antituberculars, nonsteroidal anti-inflammatory drugs, colchicine, and interleukin-1 inhibitors.

Revision #1
Created 2026-01-06 16:31:13 UTC by Omar Ayman
Updated 2026-01-06 16:31:13 UTC by Omar Ayman