Work-up of Fever of Unknown Origin in Adult Patients

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In 1961, Petersdorf and Beeson[1] defined fever of unknown origin (FUO) as persistent fever higher than 38.3°C (101°F) that lasts for 3 weeks with no established diagnosis despite 1 week of inpatient investigations. More recently, the definition of FUO has been updated to reflect developments in medicine and technology; FUO is now defined as persistent fever higher than 101°F for 3 weeks and failure to make a diagnosis with 3 outpatient visits or 3 days of inpatient investigations.[2] There are 4 subclasses of FUO: classic FUO, HIV-associated FUO, nosocomial FUO, and FUO in neutropenic patients. Each subclass has a unique differential diagnosis, and therefore each requires a different approach to diagnosis.

Given its large differential diagnosis (over 200 disorders; **Table 1**), FUO can present a diagnostic challenge to physicians. Although the work-up of FUO can be complex, a detailed history and through physical examination, along with judicious use of diagnostic procedures and good clinical judgment, will usually reveal the cause of the fever.

CLASSIC FUO

Definition and Etiology

The most common causes of classic FUO are infection (30%–40%), malignancy (20%–30%), and collagen vascular disease (10%–20%); a diagnosis is not determined in 5% to 15% of cases.[3] The diagnostic spectrum of FUO has changed over time, due in part to technological advances that have allowed for earlier diagnosis of some conditions. For example, abdominal abscesses are being diagnosed by computed tomography (CT) scans before they meet the criteria of FUO,[4,5] and collagen vascular diseases are being diagnosed more readily due to the availability of serologic tests. Since the 1950s, the proportion of FUO cases that go undiagnosed has been steadily increasing, with percentages reaching up to 30% in some surveys.[6]

Diagnostic Approach

History and physical examination. The work-up of classic FUO should be directed by the history, physical examination findings, and results of initial diagnostic tests. The first step in the evaluation should be to

TAKE HOME POINTS

- The 4 major subclasses of fever of unknown origin (FUO) are classic FUO, HIV-associated FUO, nosocomial FUO, and FUO in neutropenic patients.
- The most common causes of classic FUO are infection, malignancy, and collagen vascular disease; up to 15% of cases go undiagnosed. The initial work-up includes complete history and physical examination, blood counts, chemistry, cultures, viral serology, collagen vascular diseases serology, and computed tomography scan of the abdomen and pelvis with contrast.
- Infectious causes predominate in HIV-FUO, with disseminated *Mycobacterium avium-intracellulare* complex infection and *Pneumocystis jiroveci* pneumonia being the most common causes.
- The work-up of nosocomial FUO should be directed at ruling out infectious etiology: line sepsis, *Clostridium difficile* colitis, nosocomial pneumonia, sinusitis, and urinary tract infection. Empiric antibiotic therapy should be started immediately in immunocompromised patients and those who show signs of sepsis or pneumonia.
- In neutropenic FUO patients, inflammation may not be apparent due to the lack of leukocytes; empiric antimicrobial therapy should be instituted urgently.

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Table 1. Major Categories and Some Causes of Fever of Unknown Origin

Infections
Tuberculosis (especially extrapulmonary: renal or miliary, meningitis)
Intra-abdominal abscesses
Subdiaphragmatic abscesses
Pelvic abscesses
Osteomyelitis
Subacute bacterial endocarditis
Cytomegalovirus
Epstein-Barr virus
Toxoplasmosis
HIV infection
Chronic sinusitis
Histoplasmosis
Brucellosis
Coccidioidomycosis
Lyme disease
Malignancy
Lymphoma
Chronic leukemias
Renal cell carcinoma
Metastatic cancers
Hepatocellular carcinoma
Colon carcinoma
Pancreatic carcinoma
Myelodysplastic diseases
Autoimmune conditions
Adult Still's disease
Temporal arteritis
Polyarteritis nodosa
Rheumatoid arthritis
Systemic lupus erythematosus
Acute rheumatic fever
Familial Mediterranean fever
Sarcoidosis
Felty's syndrome
Miscellaneous
Drug fever
Factitious fever
Hyperthyroidism
Granulomatous hepatitis
Deep venous thrombosis/pulmonary embolus
Kikuchi's disease

confirm the presence of fever. The fever curve and its height as well as response to antipyretics do not seem to have a high diagnostic yield.[3] In the history, particular attention should be given to family history (eg, familial Mediterranean fever and malignancy), exposure to pets, recent sick contacts, and work environment. The travel history is important and should include an inventory of every locality visited for at least the 6 months prior to the illness as well as a complete history of travel immunization and prophylaxis received. Determining the season of travel is helpful since arthropod-borne diseases will be less common in cold conditions. Potential exposures should be sought, such as consumption of unpasteurized dairy products (brucellosis, *Salmonella*, *Campylobacter*), undercooked pork (trichinosis), or exposure to fresh water or surface water (schistosomiasis or leptospirosis). Rickettsiae, Lyme disease, ehrlichiosis, and tick-borne encephalitis should be considered in patients with history of tick bites. New sexual partner or exposure to needles raises the possibility of acute HIV or hepatitis B infection. Finally, it is important to take a complete drug history, including over-the-counter drugs, diet pills, and herbal remedies[7] **(Table 2**). Any medication can cause drug fever, even medications that the patient has been taking for months or years.

Repeated physical examination is important in FUO, as key findings can be missed on the initial examination (**Table 3**). Careful evaluation of the skin, mucous membranes, and lymphatic system must be done.

Laboratory tests. The initial diagnostic work-up includes a complete blood count with review of peripheral smear (**Table 4**), routine blood chemistry including liver function tests, chest radiography, urinalysis and culture, sputum cultures, and blood cultures. In continuous bacteremia as with endocarditis, 3 sets of blood cultures are adequate to recover organisms.[8] The erythrocyte sedimentation rate (ESR) is sensitive but not specific for infections and collagen vascular diseases. An ESR over 100 mm/h in a patient with FUO suggests adult Still's disease, temporal arteritis, endocarditis, osteomyelitis, and lymphoma; however, a normal ESR does not rule out these entities. Serologic tests for Epstein-Barr virus, cytomegalovirus (IgG and IgM), and hepatitis B and C virus should be ordered routinely for work-up of FUO. HIV antibody and HIV RNA polymerase chain reaction testing are necessary if acute HIV is suspected. In appropriate geographical settings, *Brucella* serology (Mexico, central and south America, or Mediterranean basin), *Histoplasma* serology, or urine histoplasma antigen (Ohio and Mississippi river valleys) should be considered. If collagen vascular disease is suspected, testing for antinuclear antibody, anti-dS-DNA, perinuclear antineutrophilic

Table 2. Commonly Used Medications Implicated in Drug Fever

Antimicrobials: β-lactam antibiotics (penicillins, carbapenems, cephalosporins), erythromycin, isoniazid, minocycline, nitrofurantoin, rifampin, sulfonamides
Cardiovascular agents: hydralazine, procainamide, nifedipine, quinidine, methyldopa, captopril
Anticonvulsants: barbiturates, phenytoin, carbamazepine
Nonsteroidal anti-inflammatory drugs: ibuprofen, sulindac
Others: allopurinol, cimetidine, clofibrate, herbal remedies, hydrochlorothiazide, heparin, iodides, meperidine, salicylates, bleomycin, cytosine arabinoside

Table 3. Physical Examination Findings and Associated Diseases in Fever of Unknown Origin

Dry eyes	Rheumatoid arthritis, SLE, Sjögren's syndrome
Subconjunctival hemorrhage	Subacute bacterial endocarditis, trichinosis
Uveitis	Adult Still's disease, SLE, sarcoidosis
Nodules or reduced pulsations	Temporal arteritis
Lymphadenopathy	Lymphomas, tuberculosis, cat-scratch fever, CMV, EBV, toxoplasmosis, HIV infection, brucellosis, Kikuchi's disease
Heart murmur	Subacute bacterial endocarditis
Hepatomegaly	Hepatomas, metastatic carcinoma, granulomatous hepatitis
Splenomegaly	Leukemias/lymphomas, SBE, disseminated granulomatosis
Arthritis	FMF, pseudogout, SLE, brucellosis, Lyme disease, Whipple's disease

CMV = cytomegalovirus; EBV = Epstein-Barr virus; FMF = familial Mediterranean fever; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus.

cytoplasmic antibody, cytoplasmic antineutrophilic cytoplasmic antibody, rheumatoid factor, and cryoglobulins should be performed.

Imaging studies. The choice of imaging tests should be guided by history and physical examination findings.[9] Imaging studies have been used to localize abnormalities for further diagnostic tests such as biopsy or aspiration. CT scan of the abdomen and pelvis with contrast should be one of the first investigations in FUO because it has a high diagnostic yield and will rule out most common causes of FUO, such as abscess or lymphoproliferative disorders.[10] Abdominal ultrasonography is a low-cost test that can detect abnormalities in the gallbladder and hepatobiliary system. Magnetic resonance imaging (MRI) can be more sensitive than CT scan in certain situations, such as spinal epidural abscess; however, its role in FUO has not been well established. The role of echocardiography in FUO has not been studied. However, because the Duke criteria have high specificity for endocarditis in patients with FUO,[11] echocardiography should be included in the work-up of FUO if there is suspicion of culture-negative endocarditis. Transesophageal echocardiogram (sensitivity, 100%; specificity, 98%) is preferred over transthoracic echocardiogram (sensitivity, 63%; specificity, 98%).[12,13] Venous thrombosis can present with prolonged fever. In one study, 6% of FUOs were caused by deep venous thrombosis. Duplex ultrasonography should be considered if the patient has risk factors for deep venous thrombosis.[14]

Nuclear imaging studies. The use of radionucleotide scanning is warranted for detecting inflammatory conditions and neoplastic lesions that cannot be diagnosed by CT scans. Gallium-67 scan (^{67}Ga) is particularly effective in visualizing chronic infections such as pyogenic abscess, tuberculosis, lymphomas, and sarcoidosis.[15] Radiolabeled autologous leukocyte scanning is helpful in detecting infections and malignant causes of FUO. The agents available include indium-111-labeled mixed leukocytes or pure granulocytes and technetium-99m-labeled leukocytes; current evidence suggests that these agents are equally effective, with indium-111 labeled mixed leucocytes having the advantage of easier preparation.[16] Gallium scan is more helpful than radiolabeled leukocyte scanning when the cause of an FUO is intrathoracic but less effective for intra-abdominal causes, partly because of physiologic excretion of ^{67}Ga in the gut.[15] [(18)F] Fluoro-deoxyglucose positron emission tomograph has been shown to be useful in the workup of FUO, with a diagnostic yield at least comparable to that of gallium; in addition, its results are available within hours instead of days.[17] Labeled human polyclonal immunoglobulin G so far has not been promising in evaluation of FUO.

Invasive procedures. The decision to perform an invasive procedure should be guided by the history, physical examination findings, and results of noninvasive diagnostic tests. When enlarged lymph nodes are found in an accessible position, excisional biopsy or fine needle aspiration should be considered. Liver biopsy must be considered if miliary tuberculosis or malignancy is suspected. In a study that evaluated the role of liver biopsy in diagnosis of FUO, physical findings, such as hepatomegaly, and laboratory data, including routine liver chemistries, were not predictive of a diagnostic liver biopsy.[18] Bone marrow biopsy should be considered if there is pancytopenia or abnormalities in any of the cell lines. Bone

Table 4. Blood Count Abnormalities in Fever of Unknown Origin

Leukopenia	Lupus, lymphoma, typhoid fever, chronic infections (eg, tuberculosis, brucellosis, HIV infection, rickettsial diseases)
Eosinophilia	Drug fever, trichinosis, polyarteritis nodosa
Basophilia	Lymphoma
Monocytosis	Sarcoidosis, SLE, tuberculosis, CMV, carcinomas
Lymphocytosis	CMV, EBV, toxoplasmosis
Thrombocytopenia	Leukemias, lymphomas

CMV = cytomegalovirus; EBV = Epstein-Barr virus; SLE = systemic lupus erythematosus.

marrow biopsy may provide a diagnosis in patients with lymphoma, miliary tuberculosis, or histoplasmosis, but the yield in immunocompetent patients has been low.[19] Alternatively, temporal artery biopsy is a relatively safe surgical procedure and should be considered in patients over age 55 years with a high ESR and unresolved FUO. With the advent of CT scan and other nuclear imaging studies, diagnostic exploratory laparotomy should only be considered for unresolved FUO after extensive work-up.

Therapeutic trial. Use of therapeutic interventions to make a diagnosis in FUO is discouraged. Many illnesses respond to corticosteroids only to have the disease progress with steroid-induced immune suppression. If the patient is clinically stable and no diagnosis is made after extensive work-up, it is reasonable to carefully monitor the patient. In one study, 74% of undiagnosed patients recovered spontaneously.[20]

HIV-ASSOCIATED FUO

Definition and Etiology

HIV-associated FUO is defined as recurrent fevers over a 4-week period in an outpatient setting or for 3 days in-hospital with HIV infection.[2] Primary HIV infection can present with a mononucleosis-like syndrome in which fever is a prominent feature. FUO in HIV infection usually occurs in the late stages of infection, usually with a CD4 cell count less than 100 cells/mm^3. In patients with a CD4 cell count over 200 cells/mm^3, the differential diagnosis and work-up is the same as for classic FUO, although the increased risk of tuberculosis and lymphoma must be taken into account. Infectious etiology predominates as the cause of HIV-associated FUO, accounting for 82.2% of cases in some studies.[21] In United States, the most common causes of HIV- associated FUO in patients with a low CD4 count are disseminated *Mycobacterium avium-intracellulare* (MAI) complex infection and *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia. Other causes include cytomegalovirus infection, disseminated histoplasmosis, and lymphoma.[21] In contrast *Mycobacterium tuberculosis* and leishmaniasis are the most common causes of FUO in Europe.[22] Parvovirus B19 should be considered if anemia is present. Certain diagnoses should be considered if the patient is from endemic areas or has traveled to endemic areas, such as the Ohio and Mississippi river valleys in the United States or in South America (histoplasmosis), southwest United States (coccidioidomycosis), Latin America (*Trypanosoma cruzi*), Southeast Asia (*Penicillium marneffei*), and Mediterranean basin and Latin America (leishmaniasis). Noninfectious causes of FUO in HIV patients include lymphomas, particularly non-Hodgkin's lymphoma, and drug fever (Table 2).

Diagnostic Approach

The initial approach to evaluation should include routine work-up for fever with complete blood count, comprehensive metabolic panel, and routine blood cultures. In addition, mycobacterial cultures, fungal isolator cultures, immunoassay for urine histoplasma antigen and serum cryptococcal antigen, analysis of induced sputum for *P. jirovenci* and *M. tuberculosis*; serology for endemic fungi such as *Histoplasma* and *Coccidioides*; and ophthalmologic evaluation for cytomegalovirus retinitis must be done.

CT scan of chest, abdomen, and pelvis should be done to identify lymphadenopathy (for MAI infection and lymphoma) and occult abscesses. Imaging of the brain including CT scan with contrast or MRI with gadolinium is important in patients with HIV infection to evaluate for ring-enhancing lesions (toxoplasmosis, nocardiosis, aspergillosis) or mass lesions (cryptococcoma, tuberculoma) in the appropriate clinical setting. Gallium scan is helpful in the diagnosis of lymphoma and PCP pneumonia in patients who cannot have bronchoscopy or produce sputum).

If initial tests are nondiagnostic, liver, bone marrow, or lymph node biopsy should be considered. Bone marrow biopsy usually should be done first because it is less invasive, well tolerated, and more diagnostic in patients with HIV and FUO.[23] In one series with 123 patients, culture and histopathology provided a specific diagnosis in 52 episodes, with a diagnostic yield of 37.9%. The 3 diseases diagnosed in this study were disseminated tuberculosis, MAI complex infection, and visceral leishmaniasis.[23] Percutaneous liver biopsy can be a useful procedure in patients with hepatosplenomegaly

and an elevated alkaline phosphatase level, although it should be considered only after initial work-up and bone marrow biopsy are nondiagnostic due to its invasiveness. In one study of 58 patients with FUO, liver biopsy led to a definitive diagnosis in 43.1% of patients.[24] Lumbar puncture is helpful if central nervous system symptoms such as headache or blurry vision are present. A good funduscopic examination or CT scan is necessary before performing lumbar puncture to rule out cerebral edema or papilledema. Lumbar puncturecan be helpful in diagnosing tubercular meningitis, cryptococcal meningitis, and cytomegalovirus encephalitis. Because infection is the most common cause of FUO in HIV patients, the work-up should be pursued until the cause is revealed.

NOSOCOMIAL FUO

Etiology and Definition

Nosocomial FUO is defined as fever that started more than 72 hours after admission to an acute care hospital and persists without an obvious source of infection. The etiology of the fever in this category is usually nosocomial infections, followed by drug fever and thromboembolic diseases. Most infectious causes of fever can be diagnosed with the work-up described below. Other entities to keep in mind in the work-up include drug fever, drug withdrawal (alcohol, benzodiazepine, barbiturate, methadone), transfusion of blood products (red blood cells, platelets), granulocyte-stimulating factors, chemical phlebitis, pancreatitis, acute respiratory distress syndrome, acute myocardial infarction (especially in the first few days), Dressler's syndrome (in the later phase of acute myocardial infarction or after cardiac surgery), thyroid storm, acute adrenal insufficiency, and gout.

Diagnostic Approach

Initial work-up. Physical examination should be complete with special attention to rashes (which may suggest drug fever), cellulitis, or infected pressure ulcers. Blood cultures are part of the basic work-up of nosocomial FUO, including quantitative cultures drawn from central catheters and peripheral veins if central lines are present without obvious tunnel infection. The diagnosis of line-related sepsis can be made by a colony count in blood cultures drawn from the catheter that is 10 times higher than the colony count in cultures drawn peripherally or by a difference of 2 hours or more in time to positivity between the catheter and peripheral cultures. On urinalysis, pyuria, microscopic hematuria, and positive cultures may point to a diagnosis of urinary tract infection (UTI). A positive urine culture in catheterized patients is not always associated with infection, and diagnosis of UTI in these patients should be a diagnosis of exclusion. The presence of sterile pyuria should prompt a search for eosinophiluria that would suggest a drug-induced interstitial nephritis.

A chest radiograph should be obtained to rule out nosocomial pneumonia. The presence of infiltrates can make it difficult to differentiate pneumonia from pulmonary infarct, bronchiolitis obliterans with organizing pneumonia, or even congestive heart failure. It is often necessary to obtain a CT scan of the chest without contrast, especially in patients who are ventilator dependent. If pleural effusions are present, a thoracentesis may be considered to rule out empyema. Sputum collection for Gram stain and culture can be valuable to guide antibiotic choice when pneumonia is present. Testing of stools for *Clostridium difficile* toxin should be done in patients who have received antibiotics in the recent past, even when diarrhea is not a prominent symptom; testing of stools for fecal leukocytes is sensitive but not specific for diagnosing pseudomembranous enterocolitis. Complete blood count with differential is often helpful: leukocytosis and bandemia may suggest an infectious etiology, while eosinophilia may be suggestive of drug fever. A sudden drop in hemoglobin without an obvious bleeding source or clear evidence of hemolysis suggests hematoma as an etiology for the fever. Finally, a complete metabolic profile including liver function tests can suggest the etiology. For example, a marked increase in alkaline phosphatase can suggest acalculous cholecystitis. However, increased liver enzymes can also be seen in drug-induced fever and bacteremia. Worsening renal function can point toward a drug- induced interstitial nephritis. In diabetic patients, blood glucose that becomes suddenly uncontrolled in the presence of fever should make a physician look urgently for an infectious etiology.[25]

Imaging studies. If the initial work-up is unrevealing, a CT scan of the abdomen and pelvis, with intravenous contrast when possible, should be done to look for intra-abdominal abscess, especially in patients who have undergone abdominal surgery. CT scan can also reveal a retroperitoneal hematoma and colitis suggestive of pseudomembranous enterocolitis. CT scan of the sinuses without contrast should be done to look for sinusitis, especially in patients with a nasogastric tube or nasotracheal tubes. If this approach does not lead to a diagnosis, venous Doppler ultrasonography of the lower extremities and a ventilation-perfusion scan will help to rule out a thromboembolic disease in the right setting.

Empiric Antibiotic Therapy

A systematic, diligent work-up will usually reveal the

etiology of nosocomial fever. Empiric antibiotic therapy should be started immediately in immunocompromised patients and those who show signs of sepsis or when pneumonia is suspected, but it should be stopped if an extensive work-up does not reveal an infectious source.

FUO IN NEUTROPENIC PATIENTS

Definition and Etiology

Neutropenic patients with FUO can be divided into 2 major categories: transplant patients and cancer patients on therapy presenting with febrile neutropenia. Discussion of the management of febrile transplant patients is beyond the scope of this article because most of these patients will be managed by a transplant team and will rarely be seen by residents or internists. However, febrile neutropenic patients who are undergoing chemotherapy are often seen in the emergency department, and it is critical to understand their management.

The most accepted definition for febrile neutropenia for patients receiving chemotherapy is 1 temperature of at least 101°F or 2 episodes of 100.4°F more than 1 hour apart and an absolute neutrophil count less than 500. Although infections are the most common cause of fever in neutropenic patients (and therefore antibiotics should always be started empirically), other entities that should be entertained as possible etiologies include tumor-related fever, transfusion of blood products, and drug fever. Some medications that have been implicated in drug fever include bleomycin, cytosine arabinoside, and allopurinol.

Diagnostic Approach

In approaching these patients, physicians should bear in mind 2 principles. First, signs and symptoms of inflammation may not be apparent due to the lack of leukocytes. For example, the patient may have pneumonia without obvious lung infiltrates on chest radiography or may have a UTI without pyuria. Second and more importantly, empirical antimicrobial therapy should be instituted urgently. A delay could result in the rapid death of the patient secondary to gram-negative sepsis or gram-positive organisms (eg, alpha streptococci).

With these principles in mind, a history and physical examination should be conducted promptly, with special attention to integument changes around catheter sites and the perineum (do not perform a rectal examination because this could lead to bacteremia). Blood cultures should be drawn at the earliest possible time from 2 different sites. Urinalysis with culture and sensitivity should be performed, and empirical broad-spectrum antibiotics should be started immediately after cultures have been drawn (including antipseudomonal coverage). Vancomycin does not have to be started empirically unless there is a high suspicion for line-related sepsis or severe mucositis secondary to chemotherapy or the patient had received quinolone prophylaxis for neutropenia before the onset of fever. Routine laboratory tests and chest radiograph can be performed after the antibiotics have been administered. Other tests may include a high resolution CT scan of the chest if pneumonia is suspected and the chest radiograph is negative. In addition, aspiration or biopsy of new skin lesions for Gram stain and cultures can be valuable. The 2 most common intra-abdominal infections in this setting are typhlitis and pseudomembranous enterocolitis. If the patient has abdominal pain with diarrhea, testing of stool for *C. difficile* toxin in addition to a CT scan of abdomen would be helpful. If cultures and imaging studies are unrevealing and fever with neutropenia persist beyond 4 days, empiric antifungal therapy should be started.[26]

Hepatosplenic candidiasis is classically seen in patients recovering from a febrile neutropenic episode. These patients present with fever, nausea, and vague abdominal pain; typically have negative blood cultures; and have increased alkaline phosphatase levels. The diagnosis is made by CT scan of the abdomen, which reveals multiple hypodense lesions in the liver and spleen. Aspergillosis is usually seen in patients with neutropenia lasting for more than 10 to 12 days despite receiving broad-spectrum antibiotics. Aspergillosis usually presents as sinus disease or lung involvement (ie, unresolving pneumonia, nodular or cavitary lesions). If not recognized and treated early, aspergillosis can cause rapid worsening of respiratory status with a high mortality rate.[27,28] **HP**

Test your knowledge and comprehension of this article with *Review Questions* on page 28.

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