

# Fever of Unknown Origin

## Keys to determining the etiology in older patients

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In light of improvements in imaging modalities and laboratory tests, fewer cases of fever of unknown origin (FUO) are being attributed to infectious causes and more are eventually being diagnosed as secondary to noninfectious causes, particularly tumors and connective tissue diseases. Older patients with FUO usually present with mild, nonspecific, normochromic, and normocytic anemia and an elevated erythrocyte sedimentation rate. The history, physical examination, and imaging studies are key to making a diagnosis. Although the results of laboratory tests are generally nonspecific, such tests are appropriate nonetheless. Obtaining repeat blood cultures is mandatory. However, before undertaking a diagnostic evaluation of geriatric FUO, it is important to consider the patient's overall health. In certain circumstances, it is more important to maintain a patient's quality of life than it is to initiate the process of identifying and treating a persistent fever. The work-up and treatment should not be worse than the disease.

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connective tissue disease

**F**ever of unknown origin (FUO) is a persistent (>3 wk) body core temperature of 101° F or higher for which no cause has been identified despite a reasonable amount of investigation. Since Petersdorf and Beeson published their seminal treatise on FUO in 1961, we have seen a decrease in incidence.<sup>1,2</sup> A decreased incidence occurred because there was an increase in the performance of advanced laboratory and

radiologic studies following publication of the treatise, resulting in more FUOs being diagnosed. In addition, Petersdorf and Beeson's treatise was important because it introduced and named FUO as a new diagnostic challenge.

### Causes of FUO

Subsequent to the development of highly sensitive radiologic modalities and laboratory tests, more cases of FUO

are eventually being diagnosed as secondary to noninfectious causes, such as tumors and connective tissue diseases, (table 1) as opposed to infectious causes (table 2).<sup>3</sup>

In a retrospective review of 111 FUO inpatients age 65 and older published in 1978, Esposito and Gleckman reported that the most common causes of fever were eventually found to be infection (36%), connective tissue disease (26%), and neoplasms (24%).<sup>4</sup> Miscellaneous causes were identified in 9%, and no cause was found in 5%. The most common infectious cause was abdominal abscess, which occurred in 13 of the 41 patients with infectious etiology (31.7%). Of these 13 patients, none presented with symptoms related to the abdomen, and none had a history of abdominal surgery, inflammatory bowel disease, or diverticulitis. Conversely, all 13 had a history of peptic ulcer disease and a recurrent, nonspecific urinary tract infection. All patients subsequently developed a perforated peptic ulcer or a perinephric abscess.

In 1993, Knockaert et al described a subgroup analysis of 47 FUO patients age 65 and older and found that multisystem disease—particularly temporal arteritis—was the most common cause (31%), followed by infection (25%) and tumors (12%).<sup>5</sup> Some 11% of cases were eventually attributed to miscellaneous causes, and 6% to drug fever. No diagnosis was made in 13% of cases. Most patients (77%) had an elevated alkaline phosphatase level—a

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**Table 1 Noninfectious causes of fever of unknown origin\*****Neoplasms**

Atrial myxoma  
 Leukemia, myelodysplasia  
 Liver metastasis associated with disseminated solid tumors  
 Lymphoma  
 Pancreatic cancer  
 Renal cell carcinoma  
 Sarcoma

**Connective tissue diseases**

Adult Still's disease  
 Hypersensitivity vasculitis  
 Polyarteritis nodosa  
 Primary angiitis of the central nervous system  
 Rheumatoid arthritis  
 Temporal arteritis  
 Wegener's granulomatosis

**Miscellaneous**

Alcoholic hepatitis  
 Drug fever  
 Factitious fever  
 Familial Mediterranean fever  
 Gout  
 Hematoma  
 Postmyocardial infarction syndrome  
 Recurrent pulmonary embolism, deep-vein thrombosis  
 Sweet's syndrome  
 Thyroiditis, hyperthyroidism

\* For uncommon and rare causes, refer to the source document.

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non-specific finding. Pulmonary tuberculosis was a particularly important factor in the older population, as it was identified in 20% of those who had an infectious etiology. In fact, tuberculosis was the most common disease identified in culture specimens in patients with FUO. Knockaert et al also reported that the percentage of cases for which a cause was never identified in these older patients was significantly

lower than it was in a group of younger patients in a related study (30%).

In a subsequent article published in 1996, Knockaert et al studied 199 patients of all ages with FUO and found that 61 (31%) were discharged without a diagnosis.<sup>6</sup> Of the 61, twelve (20%) were eventually diagnosed, two-thirds within 2 months of discharge. At a 5-year follow-up, mortality among patients with undiagnosed FUO was only 3.2%.

**Bacterial endocarditis**

More than 50% of all cases of bacterial endocarditis occur in patients age 50 and older.<sup>4,7</sup> According to one study, the most common finding in patients with bacterial endocarditis was a cardiac murmur (44%).<sup>4</sup> These murmurs were initially thought to be "innocent or old," meaning that these murmurs were typically caused by an underlying anatomic defect brought about by aging (eg, sclerotic valves). In older patients with FUO that was eventually found to be caused by endocarditis, mortality has been reported to be as high as 77%.<sup>4</sup> The nonspecific nature of FUO associated with endocarditis is reflected in the dismal rate of pre-mortem diagnosis—1.3% (1 in 78 cases)—reported by Esposito and Gleckman,<sup>4</sup> although by applying the Duke criteria, the incidence has increased slightly.<sup>8</sup> The cause of death was congestive heart failure in 42% of cases, arrhythmia in 30%, and unknown in 30%.

**HIV infection**

The increasing incidence of human immunodeficiency virus (HIV) infection has changed our approach to managing FUO in older patients. The growth in the number of cases of HIV infection has resulted in an increase in the incidence of reactivated tuberculosis and multidrug-resistant tuberculosis. Approximately 10% of HIV patients are age 50 or older, and the number of HIV-positive geriatric patients is expected to grow. According to one report, only 25% of geriatric FUO pa-

tients with tuberculosis have a skin test with 5 TU Mantoux.<sup>4</sup> This low figure is attributable to the age-related decline in humoral immunity.

**Connective tissue disease**

On average, 16% of cases of geriatric FUO are found to be caused by connective tissue disease, and more recent reports in the literature reflect a higher incidence.<sup>9</sup> The increased incidence is possibly attributable to the use of more sensitive serologic studies. In these patients, the most common cause of connective tissue disease is temporal arteritis (64% of cases); approximately 77% of cases of temporal arteritis occur in women.<sup>4</sup> Older patients with temporal arteritis generally present with an elevated erythrocyte sedimentation rate (ESR) (mean approximately 78 mm/hr), associated normochromic and normocytic anemia, and intermittent unilateral loss of vision. Uncommon types of connective tissue disease in older patients with FUO include granulomatous hepatitis, inflammatory bowel disease, and adult Still's disease (a form of chronic arthritis).

**Neoplasms**

Although the incidence of malignant neoplasms has been increasing, especially as our population ages, they are becoming less common as a cause of FUO in older patients, possibly as a result of improved radiologic modalities and the discovery of new cancer markers. Such FUOs can be caused by obstruction secondary to colon cancer or biliary carcinoma tumors. FUO may also be caused by neoplasms that induce pyrogens, such as Hodgkin's lymphomas and histiocytic lymphomas. Finally, FUOs can be caused by necrosis resulting from the rapid growth of a neoplasm.

Lymphoma is the most common neoplastic cause of geriatric FUO (57% of cases), followed by renal cell carcinoma, atrial myxoma, hepatoma, and carcinoma of the intestinal tract.<sup>4</sup> In their series of 26 cases of neoplasms causing FUO, Esposito and Gleckman<sup>4</sup> noted that non-Hodgkin's lymphoma

(31%) was slightly more common than Hodgkin's lymphoma (27%). They also reported that most of these tumors were diffuse histiocytic lymphomas, which are very aggressive, and that they occurred slightly more often in men (53%) than women. They reported no case of Pel-Ebstein fever (ie, periodic fever associated with Hodgkin's disease), which is rarely reported at all. All patients with lymphoma-associated FUO had anemia and an elevated ESR. In 67% of these patients, exploratory laparotomy was required to make the diagnosis; 47% had retroperitoneal lymph node involvement, 27% had isolated splenic involvement, and 27% had diffuse lymph node involvement.

### Drug fever

Of the miscellaneous causes of geriatric FUO, drug fever is the most important because the degree of alteration in pharmacokinetics and pharmacodynamics brought about by normal aging, comorbidities, and drug interactions is significant (table 3). Drug fever occurs in 3% to 5% of hospitalized patients.<sup>10</sup>

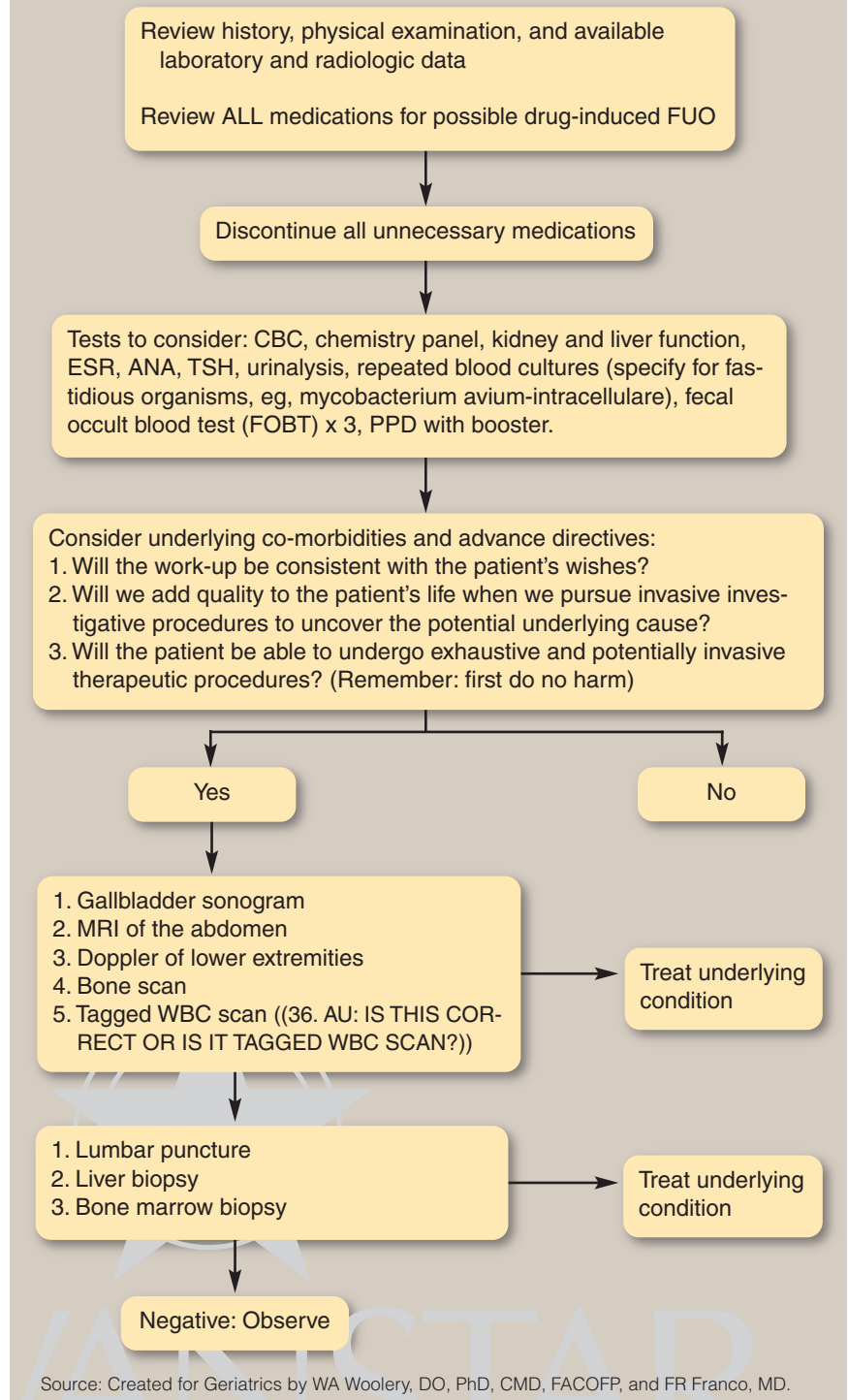
Its onset may occur 7 to 10 days following the initiation of the offending agent and resolves within 48 hours of discontinuation. Drug fever can be caused by

- route of administration,
- inherent pharmacologic action,
- direct alteration of thermoregulation,
- idiosyncratic reaction secondary to a heritable biochemical defect (eg, G6PD deficiency), and
- hypersensitivity.

Drug fever may have no characteristic pattern. The lag time between the initiation of drug and the onset of fever is highly variable. Relative bradycardia is not common (11% of cases);<sup>11</sup> when it does occur, it has diagnostic value in terms of specificity, but not sensitivity. Rash and eosinophilia are usually absent. It was once thought that women and older patients are more prone to drug fever, but this belief has since been challenged.<sup>11</sup>

The diagnostic usefulness of fever

**Figure. Diagnostic algorithm for older patients with FUO**



Source: Created for Geriatrics by WA Woolery, DO, PhD, CMD, FACOFP, and FR Franco, MD.

patterns is limited, although Johnson and Cunha reported that a double-quotidian pattern is highly specific for adult Still's disease, right-sided gonococcal endocarditis, and visceral leishmaniasis. The relative bradycardia of drug

fever and leishmaniasis is notoriously nonsensitive. Esposito and Gleckman reported a case of perinephric abscess in a patient with recurrent urinary tract infection and a case of perforated peptic ulcer in a patient with a history of

**Table 2 Infectious causes of fever of unknown origin\*****Common**

Extrapulmonary tuberculosis (eg, renal TB, meningeal TB, miliary TB)

Intra-abdominal abscess

Pelvic abscess

Subdiaphragmatic abscess (periappendiceal, pericolic, hepatic)

**Occasional**

Cytomegalovirus infection

Enteric Salmonella infection

Intra- and perinephric abscess

Splenic abscess

Subacute bacterial endocarditis

Toxoplasmosis

\* For rare causes, refer to Table 2E in the article file at [www.geri.com](http://www.geri.com).

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peptic ulcer disease.<sup>4</sup>

For patients with suspected drug fever, a rechallenge and subsequent temperature spike would clinch the diagnosis. A rechallenge is a safe way of establishing a diagnosis of drug fever unless there is an underlying cardiovascular disease. Any delay in the resolution of fever might be the result of impaired drug metabolism, delayed excretion, or tissue damage, all of which are common in geriatric patients.

**Rare causes**

In rare cases, patients have presented with both FUO and thrombosis of the iliofemoral and/or femoropopliteal veins. The author has seen two such cases in his practice during the past year. However, the author is unaware of any recent report that addresses deep-vein thrombosis (DVT) as a cause of FUO specifically in older patients. Before DVT can be considered as a possible cause of FUO, two findings must be present: 1) a positive venous duplex image for acute DVT and 2) fever resolu-

tion within 7 days of the initiation of anticoagulation therapy. In a study of 89 patients (mean age 53) with both FUO and DVT, Aburahma and Saiedy reported that 5 of 89 cases (5.6%) fulfilled these 2 criteria.<sup>12</sup> Four had iliofemoral DVT and 1 had femoropopliteal DVT, and all 5 responded well to heparin therapy. Older patients are at higher risk for complications of DVT because of their higher incidence of poor circulation, which leads to venous stasis and hypercoagulability. Moreover, aging itself is thrombogenic.

Other rare causes of FUO in older patients are familial Mediterranean fever, factitious fever, disseminated histoplasmosis, brucellosis, and vertebral body osteomyelitis. The latter can manifest only with clinical signs of nerve root or muscle compression.

**Diagnosis**

Before undertaking a diagnostic evaluation of geriatric FUO, it is important to consider the patient's overall health (figure). In certain circumstances, it is more important to maintain a patient's quality of life than it is to initiate the process of identifying and treating a persistent fever. The work-up and treatment should not be worse than the disease. Some studies suggest that PET scanning may be useful in the evaluation of patients with FUO. The diagnostic yield of this procedure in these types of patients has not been determined.<sup>13</sup>

Geriatric FUO is similar to FUO in younger adults in some respects and different in others. The physiologic changes inherent in aging make older patients unique.<sup>14</sup> Generally, older patients experience difficulty maintaining their body temperature. Their hypothalamus is less responsive to pyrogens, and they do not produce and conserve heat as efficiently as do younger patients. Overall, their body temperature is lower than normal. In older adults, a 1-degree increase from their baseline body temperature taken orally or rectally is considered a fever. With age, it becomes more challenging to define fever per se because of the physiologic temperature changes

with aging that remain uncharted.

Older patients with FUO usually present with mild, nonspecific, normochromic, and normocytic anemia and an elevated ESR. Fever presents as a non-specific cause of thromboembolic events. Evidence of peripheral embolic events has been known to manifest several months after the initial evaluation. An FUO that persists for 1 year or longer is probably caused by a connective tissue disease.

The importance of a thorough history and physical examination is self-evident. In most geriatric FUO patients, laboratory values are nonspecific and plain x-ray findings are nondiagnostic. The history and physical examination are important when looking for possible causes of FUO because they help to identify the most appropriate ancillary tests to order, such as ultrasound for suspected liver abscess.

Despite the fact that laboratory findings are often nonspecific, it is appropriate to measure the complete blood count, ESR, and antinuclear antibody level and to obtain a comprehensive metabolic panel analysis. Also, obtaining repeat blood cultures is mandatory. The physician is responsible for requesting specific tests such as DNA probes, and can issue instructions to the pathologist to look for fastidious organisms. For example, culture with Bactec can identify *Mycobacterium avium* complex (MAC) in 5 to 12 days, whereas standard culture requires 21 to 29 days. DNA probes can diagnose MAC in less than 1 hour. DNA probes are used to isolate *M avium*, *Mycobacterium tuberculosis*, and *Mycobacterium kansasii*. Also, it is important to note the relationship between *Streptococcus bovis* cultured in the blood of patients with adenocarcinoma of the colon.<sup>14</sup> An aggressive search for colonic adenocarcinoma should be initiated both during and after the diagnosis of *S bovis* bacteremia.

An upper GI series with small bowel follow-through and a barium enema is appropriate, and nuclear scanning is invaluable. Gallium scans are very sensitive in detecting bone tumors, neo-

plasma, and inflammation. An early diagnosis of osteomyelitis can be made on the basis of a technetium 99m sulfur colloid scan. An indium-labeled immunoglobulin G scan is useful in localizing occult infection, but its utility is severely limited by background activity when the liver, kidneys, or heart is the focus of study. Magnetic resonance imaging (MRI) is the study of choice for detecting lesions of the posterior and middle cerebral fossae, vertex, spinal cord, and epidural areas. Computed tomography (CT) should be reserved for follow-up evaluation of suspicious calcified and parasitic granulomatous lesions. Cerebral angiography is useful for identifying cerebral vasculitis and mycotic aneurysms.

In view of the presence of coexisting valvular heart disease in many geriatric patients, it is not practical to rely on auscultatory findings alone when looking for endocarditis; it is necessary to perform a transesophageal echocardiography when feasible. Abdominal abscesses are best evaluated by MRI, followed by CT and ultrasonography. For any pelvic pathology, ultrasonography is the preferred initial choice.

If a thorough clinical and radiologic investigation has failed to identify a cause of persistent fever, a routine biopsy of the liver and bone marrow as well as lumbar puncture should be performed. Specimens can be obtained safely in the outpatient setting.

### Conclusion

Fever of unknown origin presents a diagnostic dilemma for even the most seasoned of geriatricians. It is a diagnosis that requires an artistic blend of sound clinical judgment (which tests should be ordered) and empathic understanding of the patient (what can this individual tolerate at this point).

**Table 3** Drugs implicated as a cause of drug fever

Common	Occasional
Amphotericin B	Allopurinol
Antihistamines	Azathioprine
Asparaginase	Cephalosporins
Barbiturates	Cimetidine
Bleomycin sulfate	Cocaine derivatives
Interferon	Hydralazine HCl
Methyldopa	Iodides
Phenytoin sodium	Isoniazid
Procainamide	Nifedipine
Quinidine sulfate	Nitrofurantoin
Salicylates	Nonsteroidal anti-inflammatory drugs
Sulfonamides	Para-aminosalicylic acid
Rare	Propylthiouracil
Chloramphenicol	Rifampin
Clindamycin	Streptokinase
Corticosteroids	Streptomycin sulfate
Digitalis	Vancomycin HCl
Insulins	
Macrolide antibiotics	
Tetracycline	
Vitamins	

Source: Created for Geriatrics by WA Woolery, DO, PhD, CMD, FACP, and FR Franco, MD, based on information from references 10 and 11.

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