Fever of Unknown Origin in Older Adults

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What is fever of unknown origin?

Fever of unknown origin (FUO) means fever that does not resolve itself in the period expected for self-limited infection and whose cause cannot be ascertained despite considerable diagnostic effort [1]. In 1961, Petersdorf and Beeson [2] introduced the definition that subsequently became standard—namely, illness of more than 3-week duration, fever higher than 38.3°C on several occasions, and diagnosis uncertain after 1 week of study in hospital. Recently, Durack and Street [3] have proposed a new system for classification of FUO: (1) classic FUO, (2) nosocomial FUO, (3) neutropenic FUO, and (4) FUO associated with HIV infection. Because hospital admission is so expensive and thorough diagnostic testing now can be performed in outpatient settings, the definition recently was modified to remove the requirement that a hospital be the setting for 1 week of evaluation. The revised criteria require an evaluation of at least 3 days in the hospital, three outpatient visits, or 1 week of logical and intensive outpatient testing without determining the fever’s cause [1,3–5].

Based on these criteria, studies of FUO in the general population show that infections are the most common cause of FUO; intra-abdominal abscesses, endocarditis, and tuberculosis predominate [6]. Neoplasms and multisystem or collagen vascular diseases comprise the remaining major etiologies of FUO. The proportion of undiagnosed causes is 30% [7]. The applicability of research literature on FUO to everyday medical practice may be limited by several factors, which could include the geographic location of cases, differences in diagnostic facilities between hospitals and countries, and individual experience of the investigators and the specific subpopulations of patients who had FUO who were studied [8,9].
Studies of FUO in the elderly show that unlike in the young, a precise diagnosis can be made 87% to 95% of the time (Table 1) [10]. Often, FUO in the elderly is the result of atypical presentation of common disease. Infection is the cause in 25% to 35% of cases, with tuberculosis occurring much more commonly in elderly than young patients who have FUO. Connective tissue diseases, such as temporal arteritis (TA), rheumatoid arthritis, and polymyalgia rheumatica (PMR), account for 25% to 31% of causes in elderly patients, and malignancy accounts for 12% to 23% of all cases [10]. As many of these diseases are treatable, etiology of FUO in the elderly should be investigated further.

Medical evaluation of elderly persons requires a different perspective from that needed of younger persons. The range of symptoms is different, the manifestations of distress are less apparent, improvement sometimes is slower and less dramatic, and the implication of maintenance of function is more important. The differential diagnosis varies with age, and presentation of disease frequently is nonspecific and symptoms difficult to interpret. FUO in the elderly is an example of a classic medical syndrome that requires a specific approach.

The four categories of potential etiology of FUO in the elderly are related to patient subtype—classic, nosocomial, neutropenic, and HIV associated. Each group needs a different process of evaluation based on its characteristics and vulnerabilities. This article reviews common causes and approaches to elderly patients who have classic FUO.

### Causes of fever of unknown origin

Notwithstanding that many diseases that previously caused FUO now are diagnosed easily as a result of recent advances in diagnostic tools and
techniques, FUO remains a challenging clinical problem. The proportion of infections and neoplasms as causes of FUO has decreased over the past 40 years.

The causes of FUO traditionally have been divided into five categories: infectious, malignant, noninfectious inflammatory disease (NID), miscellaneous, and undiagnosed. The NID group has been designated differently by investigators as “rheumatic” diseases, autoimmune diseases, systemic diseases, multisystem diseases, collagen vascular disease, or vasculitides [2,7,9,10].

The lack of a uniform classification of disease hampers comparison between different series [2,5–7,11,12]. Several investigators use a separate category, namely granulomatous diseases, which also are inflammatory disorders that can be included in the NID group. In addition to classical granulomatous disorders, such as sarcoidosis and granulomatous hepatitis, they include TA, Crohn’s disease, and de Quervain’s thyroiditis in this category [11,12]. Other investigators suggest including sarcoidosis and TA in the NID category and classifying Crohn’s disease and thyroiditis in the miscellaneous group [9]. In this case, granulomatous hepatitis is not considered a disease, because it represents a histologic reaction to infections, neoplastic, and other causes. Some diseases included in the miscellaneous group have been moved to another category. A typical example is Whipple’s disease, an infection caused by Tropheryma whippelii [13]. Another example, cardiac myxoma, is a benign neoplastic disease often classified in the miscellaneous group. Moreover, Knockaert and colleagues [9,14] believe that such nonmalignant lymphoproliferative disorders as Castelman disease will be moved to another group because of evidence of the causative role of human herpes virus 8.

**Infections**

Infection is the most common diagnosis in most published series of FUO in the general population, as described in the published series of FUO in the elderly [10,15–17]. Compared with the younger population, the elderly have increased susceptibility to infection and are at significantly increased risk for morbidity and mortality resulting from many common infections.

Two earlier studies, published in 1978 [16] and 1982 [17], reported that infections (37% and 41%, respectively) and multisystem or collagen vascular disease (23% and 30%, respectively) were the leading causes of extended fevers in the elderly. In a more recent study, by Knockaert and colleagues [10], infections were less common than multisystem diseases (Table 2). This trend was even more pronounced in patients older than 70 years. Although the overall frequency of infections was the same in older and younger patients, some important differences were noted. Tuberculosis (especially in extrapulmonary sites) and abdominal or pelvic abscesses are the most common infectious diseases associated with FUO in the elderly [5].
Tuberculosis was found in 12% of elderly who had FUO, compared with only 2% of the diagnoses in younger patients, in the study by Knockaert and colleagues[10]. In this study, tuberculosis accounted for 50% of the infections in the elderly (see Table 1). In two earlier series of FUO in the elderly, tuberculosis caused 20% of the infections [16,17]. Elderly individuals seem to be at increased risk for infection, mainly because of reactivation of earlier disease. Nursing home patients are at the highest risk for this disease. Some studies show the differing presentations of tuberculosis between the elderly and younger adults. The clinical presentation often is insidious and nonspecific, as is the radiologic presentation. Symptoms, such as weakness, unexplained weight loss, failure to thrive, fever, or a change in cognitive status, may be the only manifestation of the disease[18]. Symptoms, such as hemoptysis, night sweats, and a positive purified protein derivative (PPD) test response, are less common in the elderly. Pleural effusion may be the sole manifestation of the disease. There is no difference in bacteriologically proved disease or radiologic findings between the two groups. Occurrence of miliary tuberculosis in the elderly is more common, and disseminated disease to lymph nodes, bones, kidneys, gastrointestinal tract, and skin may cause diagnostic confusion and delay [19]. The elderly who account for a large proportion of TB cases discovered at autopsy illustrate the difficulty of clinical diagnosis in this age group[18].

Intra-abdominal abscesses were found in 4% of the elderly patients who had FUO, compared with only 2% of the diagnoses in younger patients, in the study by Knockaert and colleagues [10]. In this study, tuberculosis accounted for 50% of the infections in the elderly (see Table 1). In two earlier series of FUO in the elderly, tuberculosis caused 20% of the infections [16,17]. Elderly individuals seem to be at increased risk for infection, mainly because of reactivation of earlier disease. Nursing home patients are at the highest risk for this disease. Some studies show the differing presentations of tuberculosis between the elderly and younger adults. The clinical presentation often is insidious and nonspecific, as is the radiologic presentation. Symptoms, such as weakness, unexplained weight loss, failure to thrive, fever, or a change in cognitive status, may be the only manifestation of the disease[18]. Symptoms, such as hemoptysis, night sweats, and a positive purified protein derivative (PPD) test response, are less common in the elderly. Pleural effusion may be the sole manifestation of the disease. There is no difference in bacteriologically proved disease or radiologic findings between the two groups. Occurrence of miliary tuberculosis in the elderly is more common, and disseminated disease to lymph nodes, bones, kidneys, gastrointestinal tract, and skin may cause diagnostic confusion and delay [19]. The elderly who account for a large proportion of TB cases discovered at autopsy illustrate the difficulty of clinical diagnosis in this age group[18].

Intra-abdominal abscesses were found in 4% of the elderly patients who had FUO in the study by Knockaert and colleagues [10], with the same proportion as in the younger group (see Table 1). Previous studies showed more abscesses than in Knockaert and colleagues’ study [16,17]. This can be explained by the widespread use of ultrasonography and CT that allows early detection of what had been a common cause of FUO. The locations of intra-abdominal abscesses give rise to different clinical features. Symptoms, such as abdominal pain, nausea, vomiting, or diarrhea, are common in liver or intraperitoneal abscesses or chronic cholecystitis. Reporting of tenderness

| Table 2 |
| Causes of fever of unknown origin |

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<td>Infections</td>
<td>25.5%</td>
<td>41.3%</td>
<td>36.9%</td>
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<tr>
<td>Tumors</td>
<td>12.8%</td>
<td>13.0%</td>
<td>23.4%</td>
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<td>Multisystem</td>
<td>31.9%</td>
<td>30.3%</td>
<td>25.2%</td>
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<td>10.6%</td>
<td>2.1%</td>
<td>7.0%</td>
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<td>12.8%</td>
<td>13.0%</td>
<td>5.4%</td>
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<tr>
<td>Others</td>
<td>6.4%</td>
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on examination is common in most cases of liver, splenic, or intraperitoneal abscesses. Elderly patients typically have a longer illness and a more subacute course with fewer signs and symptoms than younger patients [1]. It is suggested that the elderly do not feel pain as acutely as younger individuals or that they have less discomfort on average with a similar intra-abdominal mass, but neither of these assumptions has been proved definitively. Elderly patients who have serious, even life-threatening, intra-abdominal pathology (such as emphysematous cholecystitis, leaking abdominal aortic aneurysm, or perforated viscous) may report minimal abdominal pain. Neuropathy—especially when linked to diabetes, a common age-associated disease—and the chronic use of certain medications (such as corticosteroids or pain relievers) also may contribute to less perception of pain. Loss of abdominal wall muscle mass in the elderly patients makes guarding either impossible or less apparent [20].

Osteomyelitis is a rare cause of FUO in elderly patients. Infection reaches through the blood stream or is spread from adjacent tissue. Hematogenous osteomyelitis affects mainly the vertebrae but also may affect the long bones (eg, femur, tibia, and humerus). Hematogenous osteomyelitis almost always is a monomicrobial infection affecting predominantly the older population. *Staphylococcus aureus* is the microorganism isolated most commonly; other common pathogens include group B streptococci. Gram-negative aerobic bacilli also may be found, however, most likely caused by genitourinary tract infection or instrumentation [21]. Vascular insufficiency (eg, diabetes mellitus, atherosclerosis, or vasculitis) and neuropathy (eg, diabetes mellitus) are common factors contributing to osteomyelitis of the foot in elderly patients, involving mostly the small bones of the feet and toes. Pressure sores may be associated with underlying osteomyelitis that is difficult to differentiate clinically from infection or colonization of adjacent soft tissue. *S aureus* is a pathogen in more than 50% of the cases of contiguous-focus osteomyelitis. In contrast to hematogenous osteomyelitis, however, these infections often are polymicrobial and more likely to involve gram-negative and anaerobic bacteria. Although several bacteria often are cultured, not all of them necessarily are pathogenic. Cultures of bone specimens frequently are contaminated with organisms present in adjacent soft tissue [22]. The bacteria that are found commonly include *S aureus, S epidermidis*, streptococci, gram-negative aerobic bacilli, and anaerobic organisms. Isolation of common pathogens other than *S aureus* from sinus tracts does not reflect the pathogen isolated from bone and, therefore, a bacteriologic diagnosis of chronic osteomyelitis must be based on appropriate operative bone culture [23]. Vertebral osteomyelitis may occur through hematogenous dissemination from distant infected sources. Less commonly, in men who have urinary tract infections, aerobic gram-negative bacilli may ascend through Batson’s plexus and reach the lumbar spine. Pyogenic vertebral osteomyelitis must be differentiated from tuberculous spinal osteomyelitis, which also is common among elderly patients [24].
osteomyelitis in the general population and in the elderly are pain and fever. Pain may be absent in some of the debilitated patients who have osteomyelitis, however, because of an overlying pressure sore that does not heal and in diabetic patients who have osteomyelitis of the foot [25].

Although the frequency of infective endocarditis as a cause of FUO is low, it has become more common in the elderly. Epidemiologic studies show an upswing in the average age of patients who have infective endocarditis. Recently, 50% of these patients were found to be above 60 years of age, with a higher prevalence in men [26]. Prevalence has risen as a result of the increasing number of elderly persons who have prosthetic valves; hospital-acquired bacteremia also has become more prevalent and patients who have valvular heart disease have a longer survival rate. *Streptococci* and *Staphylococci* are the leading organisms, which are isolated from approximately 80% of elderly patients who have endocarditis. Studies show a higher prevalence of enterococci in the elderly. In addition, *Streptococcus bovis*, an organism associated with colonic malignancy, is more common in elderly patients who have endocarditis [27,28]. No significant difference in the appearance of the various pathogens within the overall general population, however, was seen in a recent study [29,30]. Endocarditis occurs more frequently on the mitral valve than it does on the aortic valve in older patients [26]. Sites of primary infection include the mouth, the genitourinary tract (particularly after procedures involving instrumentation), the skin, decubitus ulcers, surgical wound, catheters, and, rarely, the gastrointestinal tract [30]. A digestive tract portal of entry is more frequent in the elderly, however, because of the higher incidence of colonic lesions. Urologic disorders, such as prostatic or vesical diseases, also are seen more frequently in the elderly. The high incidence of these two specific portals of entry has implications for diagnosis and emphasizes the importance of prophylactic procedures during endoscopic procedures, which frequently are performed on these patients. Finally, pacemaker endocarditis is seen most often in older patients with the accompanying difficulties in diagnosis and poor prognosis [31]. The presenting symptoms of infective endocarditis in older patients may be nonspecific, such as lethargy, fatigue, malaise, anorexia, and weight loss. Heart murmurs in elderly may be attributed wrongly to the underlying valvular calcification and, therefore, overlooked. Sometimes, endocarditis in the elderly may be present with a stroke syndrome, rheumatologic complaints, or peripheral nervous system abnormalities [32,33]. Studies using the Duke criteria for diagnosis of endocarditis—frequency of fever, heart failure, embolic events, neurologic symptoms, distribution of causative organisms, and cerebral deficit—have not found any relevant differences between old and young patients at time of discharge from the hospital. Renal insufficiency and malignancy at admission, however, is found significantly more common in elderly patients who have infective endocarditis [29,30].

Viral diseases as a cause of FUO are rare in elderly patients. A few viruses, however, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and HIV, may cause FUO. Herpes viruses, CMV, and EBV, can
cause prolonged febrile illnesses with constitutional symptoms and no prominent organ manifestations, particularly in the elderly. Each of these viruses usually causes lymphadenopathies, which may be missed on physical examination if the lymph nodes are not very enlarged. Even though CMV and EBV virus infections are typical diseases of children, adolescents, and young adults, it should not be forgotten that mononucleosis also occurs in elderly patients [34]. When patients present with lymphocytosis with atypical lymphocytes, serologic testing can confirm the diagnosis. As these initially tests can be negative, it is recommended to repeat them in suspected cases 2 to 3 weeks after the onset of illness.

HIV infection is considered mainly a disease of young sexually active people and rarely was found in the elderly population. More recent studies, however, show that older persons increasingly are affected by HIV. In 1996, the Centers for Disease Control and Prevention reported that 12% of all AIDS cases were age 65 years or older [35]. Older adults may be considered at risk for HIV infection for the same reasons as the younger population: sexual activity, intravenous drug use, and blood transfusions. In addition, the elderly already may have a compromised immune system as a result of other age- and health-related conditions [36]. Primary HIV infection, disseminated Mycobacterium avium infection, Pneumocystis carinii pneumonia, CMV infection, disseminated histoplasmosis, and lymphoma are the causes of fever in HIV-infected patients reported most commonly. The various infections account for HIV-associated FUO change according to their prevalence in the different global locations [37]. HIV and AIDS may be overlooked in many cases of elderly patients even though they seem to present with the same opportunistic infections as younger patients [38]. Symptoms in this group can mimic symptoms of other diseases prevalent among them making the diagnosis difficult. Elderly patients who have AIDS and who present with symptoms of opportunistic infection often undergo the work-up and treatment for other disease processes, such as cerebrovascular disease, bacterial or viral pneumonia, malnutrition, and occult malignancy. For example, the symptoms of HIV dementia can mimic Alzheimer’s or Parkinson’s disease. Similarly, pneumocystic pneumonia may be mistaken for heart failure in the elderly who have chronic heart disease. Thus, the diagnosis of HIV infection in many cases is made late in the course of disease in older patients [37,39].

**Noninfectious inflammatory diseases**

The general term, NID, applies to systemic rheumatologic or vasculitic disease, such as TA, PMR, rheumatoid arthritis, systemic lupus erythematosus, Wegener’s disease, polyartheritis nodosa, and adult Still’s disease, and granulomatous disease, such as sarcoidosis and Crohn’s and granulomatous hepatitis [7]. This group of immune-mediated injury disorders forms the most important disease category in the study by Knockaert and colleagues
and as age increases, this trend is more pronounced. TA and PMR represent 60% of cases in this category. PMR and TA are closely related conditions and frequently occur together, affecting persons of middle age and older. Some investigators consider them to be different phases of the same disease [40]. TA is less frequent than PMR and represents 17% of the cases of FUO in the elderly patients [10]. The disease almost always is confined to Caucasians. The incidence is higher in Scandinavia and north Europe (between 17 and 18 cases per 100,000 population ages over 50 years) [41]. In Olmsted County, Minnesota, which has a high population of Scandinavian descent, the average annual incidence was 17.8 cases per 100,000 persons 50 years of age and older [42]. Autopsy studies show that giant cell arteritis may be more common than is apparent clinically [40].

The American College of Rheumatology study determined highly sensitive parameters for diagnosis of TA [43]. These parameters include (1) age at onset of disease 50 years or older, (2) new localized headache, (3) temporal artery abnormality (eg, decreased pulse, tenderness, or nodules), (4) erythrocyte sedimentation rate (ESR) greater than or equal to 50 mm per hour according to the Westergren method, and (5) abnormal temporal artery biopsy (eg, necrotizing arteritis or multinucleated giant cells). Three of five parameters are necessary for diagnosis for the purposes of classification. TA affects many arteries throughout the body, producing symptoms and signs that mimic other medical and surgical conditions. Although the fever usually is low grade in approximately 15% of patients, it can reach 39°C to 40°C and may be the presenting clinical manifestation [44]. A systemic illness with malaise, anorexia, night sweats, weight loss, and depression is common. These symptoms often are confused with infection and malignancy, resulting in delayed diagnosis that can lead to blindness or stroke developing in the meantime [45]. Arteritic involvement by inflammation is noticed most frequently in superficial temporal arteries, which may stand out and are tender when brushing hair. Atherosclerosis may be responsible for reduced or absence of pulsation; therefore, the value of the presentation of the pulsation of temporal artery is limited. Histologic detection of giant cell arteritis remains the only diagnostic investigation in TA. Normal biopsy appearances do not exclude the diagnosis because of possible skip lesions [40,41,45].

PMR appears in certain populations, with a prevalence of one case for every 133 people over the age 50 [46]. Similar to TA, the incidence of PMR increases after age 50 and peaks between 70 and 80 years of age. Population surveys show higher frequencies of PMR at higher latitudes and in Scandinavian countries and United States communities that have a strong Scandinavian ethnic background [40,42,46]. Synovitis in proximal joints and periartrial structures is shown in arthroscopic, radioisotopic, and MRI studies of patients who have PMR [40,47]. PMR is a painful condition that presents typically with pain and stiffness in the shoulders, neck, and hips that may appear suddenly. Morning or late evening stiffness is common in
both, muscles and joints. Headache, fatigue, depression, and generalized weakness may be confused with other diseases. Although tenderness on palpation of axial muscles or pain on motion of joints may be seen, physical findings usually are unremarkable. A markedly elevated sedimentation rate commonly is associated with PMR but its absence should not rule out this disease [48]. In several reports, up to 22% of patients who had PMR had an ESR that either was normal or slightly increased at diagnosis, supporting the notion that an increased ESR should not be necessary for its diagnosis. In these studies, the diagnosis was based on an otherwise typical presentation and a rapid response to a corticosteroid given in a low dose [49,50].

Tumors

Tumors are considered a common cause of FUO in the elderly. In the study by Knockaert and colleagues [10], tumors were slightly more prevalent in elderly than in younger patients but clearly less common than indicated in previous reports [16]. These tumors mainly were leukemia, Hodgkin’s disease, multiple myeloma, and colon cancer. Lymphoma was the most common neoplastic cause of geriatric FUO, followed by renal cell carcinoma, atrial myxoma, hepatoma, and carcinoma of colon in previous studies by Esposito and Gleckman [16]. In the recent study by Knockaert and colleagues [10], however, colon cancer emerged as an important cause (17% of all tumors).

Many consider paraneoplastic fever more common in primary tumors, such as renal cell carcinomas and lymphomas, but some data suggest that it occurs in tumors of diverse primary sites [51]. Among the assumed causes of tumor fever are hypersensitivity reactions, pyrogen production, primary cytokine production, and tumor necrosis with secondary cytokine production [52].

Multiple myeloma rarely causes fever and is an insignificant cause of FUO. In a series of 5523 patients who had final diagnosis of multiple myeloma who were seen at Mayo Clinic, only 9 (0.2%) had FUO caused by multiple myeloma itself [53]. Nevertheless, multiple myeloma should be included in the differential diagnosis of FUO, thereby reducing unnecessary testing, rapidly establishing the diagnosis, and initiating effective treatment.

The easy detection of solid tumors and enlarged lymph nodes by ultrasonography and CT has reduced the relative importance of tumors as a cause of FUO.

Miscellaneous group

Pulmonary embolism is an important cause of FUO in the elderly, particularly in bedridden patients, and represents 4% of the cases of FUO in this population [10]. The clinical presentations can be classified into three large groups. The first and most common presentation is dyspnea with or without pleuritic chest pain and hemoptysis. The second presentation is
hemodynamic instability and syncope, which usually is associated with massive embolism; the third and least common presentation mimics indolent pneumonia or heart failure, especially in the elderly [54,55]. Fever generally higher than 38.3°C is observed in patients who have extensive pulmonary infarction or who have secondary pneumonitis developed distal to the embolus [56].

Subacute thyroiditis with thyrotoxicosis may manifest as FUO. Although it is not a common cause of FUO, it is found consistently across several series of FUO and, together with hyperthyroidism, is the most common endocrinologic cause [57,58].

Thyrotoxicosis and the inflammation of subacute thyroiditis may cause fever. Hyperthyroidism is common in elderly individuals, although in the study by Knockaert and colleagues [10] only one patient had hyperthyroidism. In some cases, the symptoms are typical and include nervousness, palpitations, sweating, tremors, and weight loss, but often the most striking characteristic of hyperthyroidism in older patients is the lack of symptoms. They frequently do not have enlarged thyroids and do not complain of nervousness or heat intolerance. In contrast to the typical picture of weight loss despite an increased appetite, older patients may lose their desire for food and weight loss is common. Apathetic thyrotoxicosis is used to relate to patients in whom cardiovascular, myopathic, and neuropsychiatric symptoms are predominant [59]. In fact, many older patients who have hyperthyroidism are evaluated for depression or cancer before the correct diagnosis is made. Therefore, it is apparent that hyperthyroidism easily can be overlooked in the elderly, as the presenting features may not conform to the usual findings in younger people. Thus, subacute thyroiditis and hyperthyroidism should be considered in elderly patients who have FUO and elevations of ESR and alkaline phosphatase levels, even in the absence of symptoms suggestive of thyroid disease.

**Drug fever**

Drug-induced fever tends to be a difficult diagnosis, because it is confirmed only after other causes are eliminated. Diagnosis should include demonstration of the link between initiation of the drug and the start of the fever and resolution of fever within a few days of stopping the causative agent. Any pattern of fever may be seen in drug-induced fever; the mechanisms by which it occurs are numerous; and many drugs are implicated. Antibiotics are the most frequent cause of drug fever. Other classes of medication used most commonly by the elderly that cause the fever include cardiovascular drugs, nonsteroidal anti-inflammatory drugs and salicylates, histamine type 2 blockers, anticonvulsants, and psychotropic drugs. Typically, drug fever occurs 5 to 10 days after the start of treatment but it also may occur after the first dose. Although most patients are surprisingly well while febrile, some are profoundly septic. Drugs always should be considered in the differential diagnosis of FUO [1,10,60,61].
Habitual hyperthermia

Habitual hyperthermia never has been reported as a cause of FUO in the elderly and only rarely meets the criteria of FUO, because most patients who have this entity have a body temperature lower than 38°C [62].

Factitious fever

Factitious fever is a rare cause of FUO; it is more prevalent in young female patients allied with health professions and is not a cause of FUO in the elderly population in most previous studies [10,16].

Approach to elderly patients who have fever of unknown origin

Several algorithms and approaches to elderly patients who have FUO have been proposed with a staged diagnostic protocol [8–10,63,64]. The investigation of elderly patients, who have low tolerance to the long and exhausting FUO investigation, should be directed by the spectrum of underlying diseases rather than by reported results of selected diagnostic tests [10]. A reasonable approach to FUO in the elderly is to perform a thorough history and physical examination, focusing on symptoms and signs of intra-abdominal diseases, cardiac disorders, tuberculosis, musculoskeletal disorders, and cancers (Table 3). After chest radiograph and basic laboratory studies are repeated as indicated, imaging studies of the abdomen, repeated blood cultures, and echocardiography should be performed [64]. Elderly patients are more likely to have predisposing valvular conditions (eg, degenerative and calcified lesions) and prosthetic valves, which reduce the sensitivity of transthoracic echocardiography to 45%. Transesophageal echocardiography has increased the diagnostic yield of infective endocarditis in the elderly patients by 45% [27]. Early detection and treatment require a high index of suspicion and an aggressive diagnostic approach.

All nonessential drugs patients take should be discontinued immediately as should other essential drugs if fever persists. Persistence of fever beyond 72 hours after the suspected drug is removed allows the conclusion that the drug is not the cause for producing the fever [65].

Abdominal ultrasonography is a first-choice technique in investigation of FUO because of its low cost and the wealth of information it yields. CT scan of the chest and the abdomen forms the next step [10,63]. Abdominal CT scan has a major role in the detection of intra-abdominal pathology, because it has a high diagnostic value and is likely to reveal two of the most common causes of FUO: intra-abdominal abscesses and lymphoproliferative disorders [65]. These tests not only are beneficial for patients who have signs and symptoms suggesting an abdominal process but also occasionally can be useful for cases with no indication of disease elsewhere. Although this study rarely establishes a definitive diagnosis, it can help to identify abnormal tissue.
This directs clinicians to identify sites where invasive procedures, such as needle biopsy, aspiration, or catheter placement, are likely to be helpful [66]. Because of the usefulness of abdominal CT and occasionally ultrasound scanning of the gallbladder and hepatobiliary system, these tests are applied to virtually all cases of FUO. MRI should be used only for clarifying conditions found through the use of other techniques or when a diagnosis remains obscure. There is limited value in imaging techniques, such as CT and MRI, that concentrate on one area of the body if there are no localizing sign or symptoms.

Due consideration should be given to the possibility of pulmonary embolism, particularly in bedridden patients. The ventilation-perfusion lung scan is the diagnostic test used most frequently for pulmonary embolism. Non-diagnostic scans are common, however, because of the frequency of underlying cardiopulmonary disease in the elderly. A spiral or helical CT scan of the chest with intravenous contrast is sensitive and specific for diagnosis of pulmonary embolism [55].

A total body inflammation tracer scintigraphy is a valuable tool in the localization of the cause of fever. Gallium-67-citrate, labeled leucocytes (indium-111, technetium-99), labeled polyclonal human immunoglobulins
(indium-111, technetium-99), and $[^{18}\text{F}]$ fluorodeoxyglucose–positron emission tomography (FDG-PET) represent the radiopharmaceuticals investigated most intensely in the field of FUO. Newer radiopharmaceuticals, such as avidin-labeled biotin, radiolabeled liposomes, labeled cytokines, labeled specific monoclonal antibodies (specific for endothelial or leucocyte ligands), and labeled antibiotics, are under clinical development [9,67,68].

The role of the scintigraphic technique in FUO is to localize a potential cause, which then can be investigated further by ultrasonography, classical x-ray studies, CT, MRI, endoscopy, and eventually biopsy [67]. Nuclear imaging studies are helpful in localizing a potential infectious or inflammatory focus because of their minimal toxicity and overall good test characteristics [65].

The need for additional diagnostic studies should be based on abnormalities found in the initial noninvasive work-up and only when clinical suspicion shows that these tests are indicated or when the source of the fever remains unidentified after extensive evaluation should more invasive testing be performed.

High pretest probability of TA suggests that the diagnostic yield of temporal artery biopsy in older patients who have FUO (with initial negative evaluations for other causes) would be high. In particular, FUO patients older than 60 who have anemia, elevated sedimentation rate, and an elevated alkaline phosphatase level should generate a high index of suspicion for TA. A markedly elevated sedimentation rate is considered a hallmark of TA, but a sedimentation rate of less than 30 mm h is found in 10% of patients [69,70]. A positive temporal artery biopsy result confirms the diagnosis, but a negative result does not exclude it because of possible skip lesions. TA biopsy samples are positive only in 60% to 80% of patients [41]. The biopsy may exclude other systemic vasculitides, such as polyarteritis nodosa and Wegener’s granulomatosis [71]. When a biopsy is negative but clinical suspicion remains high, a contralateral biopsy should be considered even though a low diagnostic yield has been found [45,72]. Recent studies suggest that at some centers, color duplex ultrasonography may be a useful noninvasive technique for the diagnosis of TA [40,73]. A role for FDG-PET in the diagnosis of TA is proposed by Blockmans and colleagues [68,74]. As a delay in diagnosis of TA may lead to catastrophic results, such as blindness or stroke, it is essential to maintain a high index of suspicion when managing older patients at risk. Corticosteroid therapy should begin soon after obtaining initial investigations and even before performing a temporal artery biopsy in elderly patients who have FUO where there is a strong clinical suspicion of TA and serious complications, such as imminent visual loss or other vascular events. A dramatic response to glucocorticoid therapy can confirm the diagnosis [40,75].

A routine search for tuberculosis is recommended, because the presentation of tuberculosis in the elderly often is uncharacteristic in terms of symptoms and chest radiographic features [19]. Diagnosis may be difficult or even missed, hindering further treatment and cure. Because of the wide
variation in presentation of the disease in the elderly, clinicians should perform the appropriate diagnostic tests at an early stage in the disease process. The Mantoux tuberculin test is the preferred method for diagnosis of tuberculosis. The tuberculin skin tests require, however, careful interpretation because healthy elderly individuals may have positive test results as a consequence of previous infection, whereas severely ill elderly patients who have tuberculosis may be anergic and, therefore, have a negative test result. Two-step tuberculin skin test is recommended for elderly patients at high risk who have not been skin tested for many years or who never have been tested [18]. In one study, skin test responses to 5TU PPD were positive in 86.2% of young adults who had tuberculosis and only in 67.6% of elderly patients tested [19]. The lower frequency of positive tuberculin skin tests in older patients can be explained by the impairment of the immunologic responses of T lymphocytes [76]. The tests always should include sputum for smear and culture; in some cases bronchoscopy with lavage and biopsy may be needed and, rarely, open lung biopsy. Three sputum specimens, collected in the morning, should be submitted for microscopic examination. The sputum smears may be positive for acid-fast bacilli in only 50% of the cases. The use of specimens of urine and gastric lavage fluid may be hampered by the presence of mycobacterial commensals, which can cause false-positive results [18]. If disease is suspected at an extrapulmonary site, appropriate specimens should be taken for histology and culture. Two potentially useful tests often are unhelpful: the tuberculin skin test frequently is negative in the miliary and peritoneal forms, and the chest radiograph is normal in approximately 50% of most extrapulmonary tuberculosis [19]. Lung and liver biopsy each demonstrate granulomas in 80% to 90% of cases of miliary tuberculosis, and bone marrow biopsy is likely to show granulomas in only half the cases [1]. DNA amplification techniques, such as polymerase chain reaction and gene probes, may have an increasing part to play in the diagnosis of tuberculosis in the elderly [76]. The importance of tuberculosis as a cause of FUO in the elderly warrants empiric treatment with antituberculous agents if a rapid deterioration of the clinical condition occurs. Many patients are diagnosed on the basis of response to therapy alone; therefore, treatment should be started before diagnosis can be confirmed in those who have severe symptoms [63,76].

If this initial approach reveals no clues, colonoscopy, bone marrow examination, and liver biopsy should be the next steps to consider [64]. Colonoscopy, which may be uncomfortable for elderly patients, usually entails intravenous sedation and has a perforation rate of up to 0.5% [77]. The diagnostic yield from liver biopsy is 14% to 17% [78,79]. For patients in whom elevated levels of alkaline phosphatase or transaminases, or both, are documented, liver biopsy can provide evidence for a variety of malignancies and granulomatous processes. Physical examination findings of hepatomegaly or abnormal liver profile, however, are not helpful in predicting which patients will have an abnormal liver biopsy result [65]. The most
common biopsy finding is granulomas, and there may be histologic evidence of a specific cause (eg, caseation of tuberculosis, schistosomiasis, fungal organisms, or primary biliary cirrhosis) [78,79].

In immunocompetent individuals who have FUO, the diagnostic yield of bone marrow cultures is found to be 0% to 2% [80,81]. Because of the low diagnostic yield for bone marrow cultures in FUO, bone marrow cultures are not recommended in the diagnostic work-up [65]. Patients who have pancytopenia should undergo a bone marrow biopsy for histologic testing and culture. Histoplasmosis and mycobacterial infections often cause fever and pancytopenia. Bone marrow biopsy is a useful procedure for the diagnosis of FUO in patients who have advanced HIV disease, particularly in areas where tuberculosis is prevalent. Involvement of the marrow may be the first indication of the existence of extranodal lymphomas [82].

Aggressive interventions, such as explorative laparotomy, no longer are recommended if a patient’s condition remains stable. Laparotomy as a final diagnostic method for FUO cases may contribute to the diagnosis if noninvasive and invasive diagnostic measures fail. The role of surgery, however, in post-CT era remains unclear [65,68]. Laparoscopy, including laparoscopic liver biopsy, is a less traumatic alternative. It is most helpful when other features point to abdominal disease. Should such features be absent, however, the yield is only 20% [1]. Alternatively, if patients are clinically stable, it is preferable, especially in elderly patients who are more frail, to observe the patients in an ambulatory setting and repeat all noninvasive diagnostic studies at a later time or when more specific manifestations appear. After all diagnostic studies are completed, a trial of 10 to 14 days of broad-spectrum antibiotics is recommended in elderly patients who are deteriorating clinically (Fig. 1) [9,63,64]. The response to therapy is seldom proof of a single disease, as many undiagnosed FUO patients experience spontaneous resolution of fever. Alternatively, the unpredictable and often sluggish response to therapy, well known in cases of tuberculosis and endocarditis, may cause clinicians to doubt the efficacy of the therapy [9].

Summary

Elderly patients who have FUO have a different spectrum of underlying conditions. NIDs have emerged as the most frequent cause of FUO in the elderly, and TA is the most frequent specific diagnosis. Infections, in particular tuberculosis, remain an important diagnostic category. The number of cases that remain without an identified cause is significantly lower in elderly patients who have FUO compared with younger individuals. Evaluation of FUO in the elderly is complex and challenging. Atypical disease presentation is complicated further by the fact that multiple diseases commonly exist. Further, investigative procedures may be tolerated less well by older people, with decision making dependent on clinical presentation, sensitivity
and specificity of specific tests, and side effects and discomfort resulting from testing. Each patient who has FUO requires an individual approach; the use of the same algorithm in every patient is inappropriate. It is preferable to investigate the abnormalities already uncovered by others or to focus on the most likely conditions identified by unique epidemiology, age, or exposure.

FUO often is associated with treatable conditions in the elderly, and an accelerated evaluation is warranted because of the lack of physiologic reserve and risk for functional deterioration. A delay in diagnosis and initiation of appropriate treatment, therefore, may lead to increased morbidity and mortality. Early recognition and prompt initiation of appropriate empiric therapy in elderly patients, who are deteriorating clinically, are the cornerstones of the management strategy.

Finally, the physiology of thermoregulation and pathogenesis of fever is altered with advancing age, and elderly patients who have serious infections may have blunted febrile response, which may delay diagnosis and treatment. FUO in the elderly may be considered at a body temperature less than 38.3°C (at least the interval of 37.5°C –38.3°C). Within the modified definition of FUO, the relative proportion of the various etiologies in this population might change. Although there is no consensus, the authors believe that a redefinition of FUO in the elderly is required and that further studies are warranted to define the most appropriate temperature for FUO in the elderly and the causes of FUO in this group of vulnerable adults.
References


FEVER OF UNKNOWN ORIGIN IN THE ELDERLY
