Fever and Fever of Unknown Origin (FUO)

WHAT'S THE EVIDENCE for specific management and treatment recommendations?

Wright, WF, Mackowiak, PA., Mandell, GL, Bennett, JE, Dolin, R. "Fever of unknown origin". *Mandell, Douglas, and Bennett's principles and practice of infectious diseases.* Churchill Livingstone Elsevier. 2014.

- Patricia Cornejo-Juárez, - Diana Vilar-Compte

OVERVIEW: What every practitioner needs to know

Are you sure your patient has fever of unknown origin (FUO)? What should you expect to find?

- Fever of unknown origin (FUO) is defined as fever at or above 101°F (38.3°C) for 3 weeks or more that remains undiagnosed after 3 days of in-hospital testing or during two or more outpatient visits.
- FUOs, by definition, are disorders with prolonged undiagnosed fevers, but fever taken alone is unhelpful. Along with fever, other symptoms are key for an appropriate diagnosis.

- For diagnostic purposes, FUOs may be grouped into four separate categories, each with particular characteristics that orientates the diagnosis:
  - Infectious: It is frequently accompanied by chills, history should focus on invasive procedures, surgeries, oral care, antecedent/concomitant infections, pet contact, mosquito or tick exposures, blood transfusions and immunosuppressive drugs.
  - Neoplastic/malignant: Significant weight loss (>2 lbs/week), particularly accompanied by early anorexia.
  - Rheumatic/inflammatory: Arthralgias/myalgias, dry cough (clue for giant cell arteritis) or oral ulcers can help to suspect the diagnosis.
  - Miscellaneous disorders.
- FUO can also be subdivided into other categories: classic FUO, FUO associated with the human immunodeficiency virus (HIV), neutropenic FUO, and nosocomial FUO.

How did the patient develop an FUO?

- Epidemiology of FUOs varies according to the category. A comprehensive history and physical examination are cornerstone. By geographic region it's been described that in western countries, compared with other regions of the world, infections are less frequent, and inflammatory causes more common. In low and middle-income countries, enteric diseases (typhoid fever), brucellosis, tuberculosis, endocarditis, and intra-abdominal abscesses are the most commonly reported infectious causes of FUO.
- Giant cell arteritis, also known as temporal arteritis, affects Caucasians (more common in people of Northern Europe and Scandinavian descent), older than 50 years. This diagnosis could be 17% of FUO in older adults.
- The most common malignancies implicated in FUO that should be careful considered are lymphoma, hypernephroma, pre-leukemia, and atrial mixoma. Lymphomas, particularly non-Hodgkin are more frequent in HIV patients.

When considering an infectious cause of FUO, history must include:

- Previous infectious illnesses
- Family history of infections
- Similar illness in others with similar exposure
- Residence and country of origin
- Recent travel
- Zoonotic exposure
- Leisure activities.

Physical examination should pay special attention into the eyes, skin, nodes, liver and spleen.

- Eyes: Fundoscopic findings such as Roth spots, cytoid bodies, retinal hemorrhages
- Heart: Relative bradycardia, murmur.
- Spinal tenderness points
- Liver/Spleen: Hepatomegaly, splenomegaly
- Lymphadenopathy

Table I shows information on pertinent history, signs, and symptoms according to FUO category.

Table I.

History and Physical Examination Clues in FUO Work-up

Fever Patterns	Disorders Associated
Morning temperature spikes	Typhoid feverTuberculosisPeriarteritis nodosa
Relative bradycardia (pulse-temperature deficit)(Relative bradycardia should not be applied to children or those with temperatures less than 38.8°C, those on beta-blockers, diltiazem, or verapamil, or those who have pacemaker-induced rhythms or arrhythmias.)	Typhoid feverMalariaQ feverLeptospirosisCentral nervous system disorderLymphomasDrug fever
Double quotidian fevers(two temperature spikes within a 24-hour period)(Infrequent pattern. Can be useful in returning travelers.)	Miliary tuberculosisVisceral leishmaniasisMixed malarial InfectionsStill's disease
Relapsing fevers(recurring fevers separated by periods with low-grade fever or no fever)	Rat-bite feverBartonellaTuberculosisBorrelia recurrentis infectionBrucellosisCyclic neutropeniaFamilial Mediterranean feverSystemic lupus erythematosusVasculitisHyperimmunoglobulinemia D syndromeSchnitzler's syndrome
Tertian fevers(paroxysms on cycles of day 1 and 3)	Malaria (Plasmodium vivax infection)
Quartan fevers(paroxysms on cycles of day 1 and 4)	Malaria (Plasmodium malariae)
Pel-Ebstein(3-10 days episodic fevers with intervening afebrile periods of similar duration)	Hodgkin's lymphomaOther lymphomas

In evaluating FUO, fever curves, temporal and physiologic patterns of the fever are occasionally useful in suggesting a diagnosis. Table II shows fever patterns and possible causes.

Table II.

Fever Curves and Associated Disorders

FUO Category	Clues
History suggesting an Infectious disorder	Personal/family history of infectionsSimilar illness/exposureSurgical/invasive proceduresRecent travel (Asia, Africa, Latin America)Chills or night sweatsWeight lossInsect/rodent exposureZoonotic exposure
History suggesting a rheumatic disorder	Personal/family history of rheumatic disordersArthralgias/arthritisSerositisEye symptomsSplenomegaly
History suggesting a neoplastic disorder	Personal/family history of malignancyWeight loss (decreased appetite)FatigueNight sweatsAbdominal discomfort/pain
History suggesting miscellaneous disorders	Negative personal or family history for infectious, rheumatic, and neoplastic diseasesDrugs/medicationsAlcoholismInflammatory bowel diseaseThyroid/auto-immune disorders

Which individuals are of greater risk of developing FUO?

In addition to classic causes of FUO, prolonged fevers in selected populations, such as children and elderly, organ transplant recipients, HIV-infected patients, returning travelers, hospitalized patients, and patients with febrile neutropenia need to be mentioned.
Children

- Although non-infectious causes of FUO have increased in the last few decades, infections remain the most frequent cause of FUO in the pediatric population, accounting for 50% or more of the cases.
- Among infectious diseases of FUOs in children, bacterial infections remain the most common infections.
- In developing countries, brucellosis, malaria, tuberculosis, and typhoid fever are the most frequent causes of FUO. In developed countries, osteomyelitis, tuberculosis, and bartonellosis are the main causes of FUO. Epstein-Barr virus infections predominate. Cat scratch disease has increased as many children are in close proximity to cats.

- Age-related neoplastic disorders include Wilms' tumor, neuroblastoma, and lymphoma. In children, the most frequently encountered rheumatic/inflammatory cause of FUO is juvenile rheumatoid arthritis. Inflammatory bowel diseases are difficult to diagnose at an early stage but have also been described as a cause of FUO in children.

HIV

- In HIV patients with prolonged fevers, infectious causes are related to the CD4 count. The sequential appearance of opportunistic pathogens in HIV patients is well known. Frequently described infectious causes of prolonged fevers in this population include mycobacterial infections, *Pneumocystis jirovecii* pneumonia, histoplasmosis, toxoplasmosis, and cytomegalovirus. In endemic areas, visceral leishmaniasis has also been described.
- Malignancies represent about 8% of HIV fevers of unknown origin. Lymphomas, especially non-Hodgkin's lymphomas are the most frequent non-infectious cause of fever in HIV patients. Other cancers such as bronchogenic carcinoma and hepatoma, are increasingly common in this population.
- Drug fever is common (3-20%). Drugs commonly involved include antimicrobials (trimethoprim-sulfamethoxazole, beta-lactamase, sulphonamides, Sulfa containing laxatives) and diuretics; highly active antiretroviral therapy (HAART) drugs have become increasingly important.
- Immune reconstitution inflammatory syndrome (IRIS) occurs usually in the first 60 days after initiating HAART, it's frequently associated to with an inflammatory condition. Infection-associated clinical manifestations are common, and are important clues to the diagnosis of IRIS in HIV patients.

Organ transplant recipients

- In transplant recipients, the diagnostic approach is based in important factors: degree and duration of immunosuppression time of post-transplant FUO (from 1-6 months, and >6 months), recent or remote epidemiological exposure, and clinical manifestations.
- Immunosuppression status is based on several markers: additive immunosuppressive therapy, associated neutropenia, renal failure, diabetes, graft versus host disease and coinfection with other immunosuppressive virus (cytomegalovirus, Epstein-Barr virus, HIV).
- There are non-infectious causes including neoplastic disorders secondary to immunosuppression, pulmonary emboli, transplant rejection and drug fevers.

Elderly

- Studies of FUO in the elderly show that unlike the young, a precise diagnosis can be made 87-95% of the time. Often, FUO in the elderly is the result of atypical presentation of common diseases.
- Infection is the cause in 25-35% of cases, with tuberculosis occurring much more frequently than in young patients (12 vs. 2%, respectively). Connective tissue diseases, such as temporal arteritis, rheumatoid arthritis, and polymyalgia rheumatica account for 25-31% of causes. Malignancy accounts for 12-23% of all cases.

Febrile neutropenia

- In patients with febrile neutropenia and prolonged fever, consider common causes, such as central venous catheter-associated infections. If a patient with febrile neutropenia remains febrile and has prolonged fevers after a week of antimicrobial therapy, invasive

fungal infection due to *Candida spp*. or *Aspergillus spp*. needs to be assessed. If the patient develops right upper-quadrant pain with an otherwise unexplained increase in alkaline phosphate, hepatosplenic candidiasis should be considered. Febrile neutropenic patients may also develop small pulmonary emboli as an obscure cause of fever.

Hospitalized patients

- The prevalence of FUO in hospitalized patients is reported to be 2.9%, and infections remain the most frequent cause. In these patients, the most common causes are endocarditis related to a device or procedure, central venous catheter-associated infections, and *Clostridium difficile*colitis. Non-infectious causes include deep venous thrombosis, pulmonary emboli, and drug fevers.

Returning travelers

- Prolonged fevers in returning travelers reflect the epidemiology of the area that was visited. A detailed epidemiologic history is of utmost importance including visited/duration of stay, food exposures, insect exposure and bites, and time elapsed after their return. The most common infectious diseases of prolonged fevers in this population include: enteric infections, malaria, dengue, chikungunya and leishmaniasis. Zika is increasing in many regions of the Americas and needs also to be considered.
- In travelers on long aircraft flights, deep venous thrombosis and pulmonary emboli are also a cause of fever.
- In Table III, causes of FUO are listed and grouped.

Table III.

Classic Causes of Fever of Unknown Origin

Category	Very Common	Common	Common	Uncommon
Infectious diseases	Intraabdominal, pelvic, renal, and perinephric abscessSubacute bacterial endocarditisTyphoid/enteric feversMiliary, renal, and meningeal tuberculosis	Epstein-Barr's mononucleosis (elderly)CytomegalovirusCat scratch disease (children and young adults)	Epstein-Barr's mononucleosis (elderly)CytomegalovirusCat scratch disease (children and young adults)	ToxoplasmosisQ feverLeptospirosisHistoplasmosisCoccidiomycosisTrichinosisRelapsing feverRat bite feverLymphogranuloma venereumChronic sinusitisRelapsing mastoiditisSubacute vertebral osteomyelitisWhipple's disease
Rheumatic/inflammatory disorders	Adults Still's diseasePolymyalgia rheumatic/temporal arteritis	Late onset rheumatoid arthritisSystemic lupus erythematosusPeriarteritis nodosa/microscopic polyangitis	Late onset rheumatoid arthritisSystemic lupus erythematosusPeriarteritis nodosa/microscopic polyangitis	Takayasu's arteritisKikiuchi's diseasePolyarticular goutPseudogoutFamilial Mediterranean feverSarcoidosis
Neoplastic disorders	LymphomasHypernephromas	Hepatomas/liver metastasesMyeloproliferative disorders (chronic lymphocytic and myelogenous leukemia)Acute myelogenous leukemiaColon cancer	Hepatomas/liver metastasesMyeloproliferative disorders (chronic lymphocytic and myelogenous leukemia)Acute myelogenous leukemiaColon cancer	Atrial myxomasPrimary and metastatic central nervous tumorsPancreatic carcinomas
Miscellaneous	Drug feverAlcoholic cirrhosis	Crohn's diseaseSubacute thyroiditis	Crohn's diseaseSubacute thyroiditis	Deep venous thrombosis/pulmonary embolismHypothalamic dysfunctionPseudolymphomasSchinitzler's syndromeHyper-IgD syndromeFactitious fever

Other causes

In addition to classic causes of FUO, newly emerging diseases should be considered. Some of FUO causes in this group are either known diseases infrequently seen, or newly disorders

described as FUO. Because of increased travelling, entities commonly recognized and diagnosed in the endemic areas are not recognized with their clinical presentation in non-endemic areas (e.g., melioidosis, leishmaniasis, Chikungunya fever).

- In children, infections caused by Bartonella and Picornavirus are increasingly diagnosed.
- In the elderly, Epstein-Barr virus and cytomegalovirus infections should be considered in patients with prolonged and perplexing fevers, along with non-infectious causes, such as chronic myelogenous leukemia, acute lymphocytic leukemia, and rectal carcinoma.

What laboratory studies should you order and what should you expect to find?

Results consistent with the diagnosis

The relative frequency of the causes of FUO in each category is the basis for a phased diagnostic approach. The initial approach can be divided in three phases.

Phase I: Relevant history, physical examination, and non-specific laboratory tests. The findings in the initial phase of evaluation suggest which general category of disorder might be responsible for the patient's FUO.

Basic non-specific laboratory test battery on the initial phase of evaluation of FUO includes:

- Comprehensive history and physical examination
- Complete blood count (CBC)
- Blood film reviewed by hemopathologist
- Erythrocyte sedimentation rate
- C-reactive protein
- Liver function tests
- Blood cultures
- Urine cultures
- Chest radiograph
- CT and MRI scans of the abdomen and pelvis (as dictated by clinical clues suggesting intra-abdominal or pelvic pathology)

Phase II: During the second phase of FUO evaluation, focused diagnostic approach uses a more detailed history, physical examination, and additional nonspecific laboratory tests.

Laboratory tests in the focused test battery during FUO evaluation include:

- Antinuclear antibodies
- Rheumatoid factor
- Serum protein electrophoresis
- Serum ferritin
- Cold agglutinins
- Epstein-Barr, Cytomegalovirus and Bartonella serology
- Hepatitis serology (if abnormal liver enzyme tests result)
- HIV serology

Additional laboratory tests according to signs and symptoms also include:

- If lupus erythematosus is suspected:

    - Double stranded DNA
    - Anti-Smith antibodies
- If malignancy is suspected:
    - Uric acid
    - Lactate dehydrogenase
    - Leukocyte alkaline phosphatase
    - Beta-2 microglobulin
- If subacute thyroiditis is under consideration:
    - Thyroid function tests
    - Thyroid antibodies
- In patients with a heart murmur:
    - Transthoracic and transesophageal echocardiography

Phase III: Definitive diagnostic testing is conducted in this final phase. The disorders not diagnosed to this point are uncommon causes of FUO and invasive diagnostic testing (Table IV), or tissue biopsy is required. Lymph node biopsy is the most frequent invasive test. If bone or marrow involvement is likely, bone marrow biopsy and culture may be diagnostic. With image directed percutaneous biopsies, the necessity for exploratory laparotomy has been largely eliminated. Nowadays, exploratory laparotomy is useful primarily to obtain lymph node or organ biopsies that are otherwise unobtainable.

Table IV.

Invasive Diagnostic Tests for Definitive FUO Evaluation

Invasive Procedure	Most Useful for "X" Type of Disease
Liver biopsy	Granulomatous hepatitisGranulomas caused by infections, rheumatic-inflammatory disorders, or neoplasias
Lymph node biopsy	LymphomasLymphogranuloma venereumToxoplasmosisKikuchi's arteritisGranulomas (may represent a granulomatous disorder [tuberculosis, sarcoidosis] and lymphoma)
Bone marrow biopsy	Neoplastic disordersIntracellular infections (e.g., disseminated histoplasmosis)Miliary tuberculosisMiscellaneous disorders (e.g., temporal arteritis)
Exploratory laparotomy	Guided by clinical syndromic presentation and the pattern of physical and laboratory abnormalities, as well as the pattern of organ involvement

What imaging studies will be helpful in finding the cause of FUO?

Imaging tests should be ordered as dictated by clinical clues and in accordance to the phased diagnostic approach shown above.

- CT or ultrasonography of the abdomen should be one of the first investigations in FUO. It has a high diagnostic yield and is likely to identify two of the most common causes of FUO: intra-abdominal abscess and lymphoproliferative disorders. These studies may also be useful for cases with no indication of disease elsewhere, helping the clinician to identify sites in which invasive procedures are likely to be helpful. In the United States, the average cost of an abdominal CT scan is $2175. The cost of an ultrasound is approximately $390.
- In bedridden patients, a ventilation-perfusion lung scans or a helical CT scan of the chest with intravenous contrast should be ordered if there is a possibility of pulmonary embolism. Ventilation-perfusion lung scans are usually more expensive than helical CT scans.
- Total body inflammation tracer scintigraphy is a valuable tool in the localization of the cause of fever. Technetium-99 and Indium 111-labeled white blood cells (WBC) scans have been reported with the highest specificity (69-94%) and seem to be the most useful for detecting infectious causes of fever, such as osteomyelitis. Nuclear medicine scans are usually not as expensive as other tests, and have a good diagnostic yield.
- (^{18}F) Fluorodeoxyglucose-positron emission tomography (FDG-PET) appears to be of great advantage, because malignancy, inflammation, and infection can be detected; it has good sensitive and the diagnosis can be obtained much earlier than with other radiotracer techniques. Hybrid imaging (PET-CT or PET-MRI) improves the diagnostic impact of FDG-PET. The cost and availability of this imaging technique can be a disadvantage. In the United States, the cost of a PET-Scan varies between $2000 and $5000.
- Transthoracic echocardiography or transesophageal echocardiography should be obtained in all patients with a heart murmur and persistent bacteremia due to known endocarditis pathogens or in those with negative blood cultures with peripheral manifestations of endocarditis. The transesophageal echocardiography is an invasive procedure and should be ordered in patients with high suspicion of bacterial endocarditis. Its cost in the United States is about $3700.

What consult service or services would be helpful for making the diagnosis and assisting with treatment?

The disorders responsible for FUOs are numerous, and multiple specialties are frequently involved in the diagnostic approach; however, a detailed history and physical examination usually suggests a specific FUO category. Infectious Diseases specialists, Rheumatologists, Haematologists and Oncologists are frequently involved during the diagnostic work-up. Depending on the signs and symptoms, Pulmonologists and Surgeons may be involved as well. Radiologists, Nuclear Medicine physicians, and Pathologists play a key role.

Independently of the cause of the fever, neither physicians nor patients must attempt to lower the fever, because it is a cardinal sign. Antipyretics should be avoided because obscures the febrile response and alter fever patterns that may be important diagnostically.

FUO without a precise diagnosis after intensive investigation and prolonged observation usually carries a favorable prognosis. Most causes of FUO are usually not rapidly progressive, and appropriate therapy can be initiated after the diagnosis is confirmed.

Empiric therapy

The utility of empiric therapy, such as antibiotics, anti-tuberculosis agents, or corticosteroids, has not been studied in classical FUO but is not an uncommon practice. In certain situations, empiric therapy is reasonable and necessary. It is recommended in only four situations:

1. Antibiotics for culture-negative endocarditis

Between 45 to 70% of patients with infective endocarditis cases without a microbiological diagnosis, had received antibiotics before blood cultures are drawn. Up to 31% of cases of infective endocarditis have sterile blood cultures, but truly culture-negative endocarditis accounts for a small percentage of infective endocarditis (around 5%). The modified Duke criteria have become the mainstay for diagnosis of infective endocarditis.
Obligate intracellular bacteria, fungi, and fastidious organisms, including bacteria belonging to the HACEK group (*Haemophilus aphrophilus, H. paraphrophilus, H. parainfluenzae, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella* spp.), and *Abiotrophia* spp. are recognized causes of bacterial endocarditis. The epidemiology of culture-negative SBE has been changing in the past few years. Recent case series report *Coxiella burnetii, Bartonella, Chlamydia, Legionella*, and *Mycoplasma* spp. as the likely cause in up to 24% of cases of culture-negative endocarditis or 2-3% of all cases of infective endocarditis.

There is general agreement that a regimen for empiric therapy should be appropriate for enterococci, nutrient-variant streptococci, and fastidious gram-negative bacilli of the HACEK group.

2. Corticosteroids for presumed temporal arteritis

Management of suspected temporal arteritis is vital and may prevent blindness or cerebrovascular disease. Vasculitic doses of corticosteroids (40-60 mg qid) should be used in the treatment of such patients. For patients with blindness, a methylprednisolone bolus has been recommended.

In some cases, the addition of aspirin should be considered to prevent ischemic cerebral complications. Methotrexate or a TNF-alpha blocker can be used in cases refractory to steroids or in those in whom a decrease of corticorsteroids is needed because of adverse effects. Azathioprine, cyclophosphamide, dapsone, and imatinib have also been used.

3. Antituberculous drugs for suspected miliary tuberculosis

Miliary tuberculosis is a difficult diagnosis to confirm and usually requires biopsy of liver or bone marrow. If miliary tuberculosis is suspected and the patient is deteriorating clinically, empiric anti-tuberculosis therapy is reasonable and may be life-saving.

Empiric trial of antituberculous therapy includes four drugs (isoniazid, rifampin, pyrazinamide, and ethambutol, in accordance with weight), at least until biopsy results are available. This diagnosis should be suspected, especially in elderly patients who present with an afebrile wasting illness; in febrile patients with HIV/AIDS; in patients with rheumatoid arthritis treated with corticosteroids, methotrexate, or infliximab; and in recipients of solid organ transplants.

4. Naproxen for suspected neoplastic fever

Most neoplasms are associated with no or low-grade grade fever, with important exceptions: lymphomas, hypernephromas, pre-leukemia and atrial myxoma.

When the main differential diagnosis is between neoplastic and infectious disorders, some authors have suggested adding a Naprosyn test (Naproxen 375 mg by mouth bid for 3 days) as a part of the diagnostic workup. If temperature decreases markedly, then a malignant disorder is likely (positive Naprosyn test). If fever remains elevated or only slightly decreases, an infectious aetiology is likely (negative Naprosyn test). There is no good theoretical explanation as to why Naproxen lyses fever caused by neoplasms and not for fever from other causes. The Naprosyn test should be used infrequently and must be interpreted with caution.

What complications could arise as a consequence of FUO? What should you tell the family about the patient's prognosis?

- Prognosis of FUO is determined by the cause of the fever and by the nature of the underlying disease(s). Elderly patients and those with neoplastic diseases have the poorest prognosis. Children without a discernible cause, eventually, do better than adults.
- FUOs that remain undiagnosed over long periods of time are unlikely due to an infectious or neoplastic etiology. Undiagnosed FUOs may be recurrent or persistent. After a focused work-up, an undiagnosed FUO of prolonged duration is usually due to a miscellaneous cause, including periodic fever syndromes not discussed in this review. Those cases in which a precise diagnosis is not made after intensive investigation and prolonged observation usually show a favourable prognosis.
- Among all the categories of FUO, rheumatic inflammatory diseases are the most likely to manifest as recurrent FUOs.