Fever of unknown origin

INTRODUCTION

- Clinicians commonly refer to a febrile illness without an initially obvious etiology (sometimes called fever without localizing signs) as fever of unknown origin (FUO).
- This usage is not accurate. Most febrile illnesses either resolve before a diagnosis can be made or develop distinguishing characteristics that lead to a diagnosis.
- FUO refers to a prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing.

DEFINITION

- The definition of FUO derived by Petersdorf and Beeson in 1961 from a prospective analysis of 100 cases has long been the clinical standard
- ●Fever higher than 38.3ºC on several occasions
- ●Duration of fever for at least three weeks
- ●Uncertain diagnosis after one week of study in the hospital
- not immunocompromised (neutropenia for ≥1 week in the 3 months prior to the start of the fever; known HIV-infection; known hypogammaglobulinemia or use of 10 mg prednisone or equivalent for ≥2 weeks in the 3 months prior to the start of the fever)

- Refinements to the definition have been proposed, including eliminating the in-hospital evaluation requirement because of the increased expense of inpatient care and sophistication of outpatient evaluation .
- Expansion of the definition has also been suggested to include health care-associated, neutropenic, and HIV-associated fevers that may not be as prolonged

- The revised definition proposed by Durack and Street in 1991 divided cases into four distinct subclasses: classic FUO, nosocomial FUO, neutropenic FUO, and HIV-related FUO.

- **Establishing that a patient has an FUO** — As noted above, the degree and duration of fever are not the only criteria for defining an FUO. Prior to concluding that a patient has an FUO, the following evaluation should have been performed and should have been unrevealing:
- ●History
- ●Physical examination
- ●Complete blood count, including differential and platelet count
- ●Blood cultures (three sets drawn from different sites with an interval of at least several hours between each set; in cases in which antibiotics are indicated, all blood cultures should be obtained before administering antibiotics)
- ●Routine blood chemistries, including liver enzymes and bilirubin
- ●If liver tests are abnormal, hepatitis A, B, and C serologies
- ●Urinalysis, including microscopic examination, and urine culture
- ●Chest radiograph
- If any signs or symptoms point to a particular organ system, further testing, imaging, and/or biopsy should be pursued

ETIOLOGY

- **COMMON CAUSES**
- Three general categories of illness account for the majority of "classic" FUO cases and have been consistent through the decades
- ●Infections
- ●Connective tissue diseases (eg, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica)
- ●Malignancies
- Worldwide, the proportion of FUO due to infection, connective tissue disease, malignancy, and other etiologies varies substantially, based on geography, patient-population, health care exposure, and other factors.

- **Infections** — Infectious etiologies vary by geography and are especially predominant in certain areas of the world, such as southeast Asia .
- In a systematic review and meta-analysis that included 832 cases of FUO ultimately attributed to a specific infectious etiology, tuberculosis was the most common worldwide infectious cause (34 percent). Other common causes included brucellosis (10 percent; isolated to southern Europe, eastern Mediterranean, southeast Asia, and western Pacific), endocarditis (8 percent), and abscess (7 percent). Other notable causes were herpesviruses (eg, cytomegalovirus, Epstein-Barr virus), pneumonia, urinary tract infections, and enteric fever. The Americas and Africa were underrepresented in the studies included in the review.

- **Tuberculosis** — Tuberculosis (TB) is the single most common infection in most FUO series . Presentations of TB, which escape early detection, are either extrapulmonary, miliary, or occur in the lungs of patients with significant preexisting pulmonary disease or immunodeficiency.
- The purified protein derivative skin test is positive in fewer than 50 percent of patients with TB who present with an FUO, usually due to cutaneous anergy. The interferon-gamma release assay also has low sensitivity for the diagnosis of active TB. Sputum samples are positive in only one-quarter of cases. Because of these difficulties, establishing the diagnosis often requires biopsy of affected nodes, bone marrow, or liver.
- Techniques for isolation of *Mycobacterium tuberculosis* from blood include isolator cultures and polymerase chain reaction (PCR) on BACTEC blood culture bottles with evidence of early growth. Both of these methods have yielded positive results in approximately 16 days, although PCR may be more sensitive and specific.

- **Abscess** — Occult abscesses are usually located in the abdomen or pelvis. Underlying conditions, which predispose to abscess formation, include cirrhosis, steroid or immunosuppressive medications, recent surgery, and diabetes. Abscesses arise when there has been disruption of a barrier such as the bowel wall in appendicitis, diverticulitis, or inflammatory bowel disease. The rupture often seals off spontaneously and local peritonitis is converted to an abscess by host defense mechanisms. Intraabdominal abscesses can develop in subphrenic, omental, pouch of Douglas, pelvic, and retroperitoneal locations in addition to visceral sites.
- The source of infection in these abscesses can vary with the site of abscess formation:
- ●Pyogenic liver abscesses usually follow biliary tract disease or abdominal suppuration such as appendicitis or diverticulitis. Amebic liver abscesses cannot be distinguished on clinical grounds from pyogenic abscesses; amebic serology is positive in more than 95 percent of cases of extraintestinal disease.
- ●Hematogenous seeding rather than contiguous spread accounts for the majority of splenic abscesses, which are often missed prior to autopsy; endocarditis is the most common infection currently associated with splenic abscess.
- ●Perinephric or renal abscesses usually arise from existing infection in the urinary tract, although urine cultures may be negative or only intermittently positive.
- **Osteomyelitis** — Osteomyelitis should be considered as a cause of FUO since localized symptoms in some sites may not be prominent. Examples include vertebral osteomyelitis and osteomyelitis of the mandible.

- **Bacterial endocarditis** — Cultures are negative in 2 to 5 percent of patients with infective endocarditis even when the utmost care is taken in obtaining the proper number and volume of blood cultures. The frequency of negative cultures is higher in patients who have already been treated with antimicrobials, such as intravenous drug users who frequently self-administer antibiotics .
- Culture negativity is particularly likely with the following organisms, which are more difficult to isolate in culture:
- ●*Coxiella burnetii* (Q fever) and *Tropheryma whipplei* occasionally cause endocarditis but will not grow using cell free media.
- ●*Brucella*, *Mycoplasma*, *Chlamydia*, *Histoplasma*, *Legionella*, and *Bartonella* will not grow unless special media or microbiologic methods are employed.
- ●*Haemophilus* spp, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* (the so-called HACEK group) will not be detected unless blood cultures are incubated for 7 to 21 days.

- The microbiology laboratory should be notified when endocarditis or other infections with such organisms are suspected, since most laboratories routinely discard blood cultures when there has been no growth after seven days of incubation.
- Nonculture-based diagnostic modalities can be used to increase the diagnostic yield when culture-negative endocarditis is suspected (eg, serologic assays or polymerase chain reaction).
- Peripheral manifestations are rarely detected in subacute endocarditis presenting as FUO. Endocarditis in intravenous drug users is often right sided and lacks murmurs, and self-administration of antimicrobials may obscure the detection of bacteremia.
- Transesophageal echocardiography is positive in over 90 percent of cases of infective endocarditis presenting as FUO . False-positive results may be due to anatomic abnormalities or noninfective vegetations; false-negative results occur with small vegetations or those that have already embolized.
- Rarely, other endovascular infections (eg, mycotic aneurysms, septic thrombophlebitis) can be occult causes of fever

- **Less common infections**
- **Dental abscess** — Apical dental abscesses are a rare cause of persistent fever that can be overlooked by the patient and physician. Among the 20 case reports in the literature, most individuals defervesced following removal of the decayed teeth, with or without antimicrobial therapy. Other conditions linked to oral disease include brain abscesses, meningitis, mediastinal abscesses, and endocarditis; these are more common than dental FUO.
- **Other infections** — Tickborne illnesses are becoming more prevalent and more widely distributed in the United States. Organisms that cause babesiosis, Lyme disease, and anaplasmosis/ehrlichiosis, which have varying incubation periods and different susceptibilities to antimicrobial agents, may infect an individual concurrently or serially and present as FUOs or relapsing fever syndromes. Furthermore, emerging pathogens such as *Borrelia miyamotoi* may further confound diagnostic efforts.
- A number of more obscure infections that are associated with FUO and usually have a pulmonary component include Q fever, leptospirosis, psittacosis, tularemia, and melioidosis. Other less common infections that cause FUO but do not have pulmonary manifestations include secondary syphilis, disseminated gonococcemia, chronic meningococcemia, visceral leishmaniasis, Whipple's disease, and yersiniosis.

- **Connective tissue diseases**
- Adult-onset Still’s disease in young and middle-aged adults and giant cell arteritis (GCA) in older individuals are the most common rheumatologic disorders presenting as FUO. GCA accounts for approximately 15 percent of cases of FUO in older adults .
- **Adult-onset Still’s disease** — Adult-onset Still’s disease is an inflammatory disorder characterized by quotidian (daily) fevers, arthritis, and an evanescent rash. Patients with adult-onset Still’s disease have features similar to children with systemic juvenile idiopathic arthritis.
- **Giant cell arteritis** — The diagnosis of GCA should be considered in a patient over the age of 50 who complains of headache, abrupt loss of vision, symptoms of polymyalgia rheumatica (which can occur without signs of vasculitis), unexplained fever or anemia, and a high erythrocyte sedimentation rate. The manifestations of GCA, however, can vary and may be transient. Jaw claudication, if present, is helpful in suspecting the diagnosis of GCA. Temporal artery biopsy is suggested in all cases of suspected GCA.
- **Other** — Other rheumatic disorders also may present as an FUO, including polyarteritis nodosa, Takayasu's arteritis (which is common in Japan), granulomatosis with polyangiitis, and mixed cryoglobulinemia.

- **Malignancy**
- The most common malignancies to present with FUO are as follows:
- ●Lymphoma, especially non-Hodgkin's
- ●Leukemia
- ●Renal cell carcinoma
- ●Hepatocellular carcinoma or other tumors metastatic to the liver

- The most frequent occult malignancies to cause fever are of reticuloendothelial origin (eg, lymphoma and leukemia). Fever is most often evident in advanced lymphomas or in those with aggressive histologic patterns. Computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis and bone marrow biopsy usually identifies the sites of involvement.
- Myelodysplastic syndromes occasionally present with fever and subtle evidence on blood smear of maturation arrest or dysplastic changes in one or several of the blood cell lines. Aleukemic leukemias are usually of the myeloid line. The diagnosis is made by bone marrow biopsy. Multiple myeloma has also been reported as a cause of FUO .
- Renal cell carcinoma presents with fever in approximately 20 percent of cases. Microscopic hematuria and erythrocytosis may occur, but frequently there are no urine sediment abnormalities and the hematocrit is normal. Other adenocarcinomas also can cause fever, often but not invariably in the presence of hepatic metastases.
- Atrial myxomas are uncommon but present with fever in approximately one-third of cases. Other findings include arthralgias, emboli, and hypergammaglobulinemia. The diagnosis is usually established by echocardiography.

- **Drugs** — Drugs can cause fever by stimulating an allergic or idiosyncratic reaction or by affecting thermoregulation. Eosinophilia and rash accompany drug fever in only 25 percent of cases; thus, the absence of these findings should not preclude a search for a possible offending drug.

- **LESS COMMON CAUSES**
- **Factitious fever** — Factitious fever is usually a manifestation of an underlying psychiatric condition that predominantly affects women and healthcare professionals. Patients with factitious fever feign illness for some secondary gain. They may also display evidence of self-mutilation and may have had multiple hospitalizations, invasive diagnostic tests (eg, cardiac catheterization), and surgery. The response to psychiatric intervention has been discouraging.
- Fever elevations may be fabricated through manipulation of thermometers. Manipulated temperature elevations can be extreme, sometimes exceeding 41ºC, and the fever cycles may not be accompanied by the expected patient behavior and physical signs such as chills, covering with blankets, cool extremities, sweats, warm extremities, and tachycardia. Current widespread use of electronic thermometers diminishes the opportunity to manipulate or exchange thermometers.
- Fever also can be induced by taking medications to which patients are allergic (eg, phenolphthalein) or by injecting foreign matter parenterally (eg, milk, urine, culture material, feces). The resulting illness may be associated with polymicrobial bacteremia, episodes of bacteremia caused by different pathogens, or recurrent soft tissue infections.

- **Disordered heat homeostasis** — Disordered heat homeostasis occasionally follows hypothalamic dysfunction (eg, following a massive stroke or anoxic brain injury) or abnormal heat dissipation (from skin conditions such as ichthyosis). Excess heat production may also occur from illnesses such as hyperthyroidism.
- **Alcoholic hepatitis** — The characteristic signs and symptoms of alcoholic hepatitis are fever, hepatomegaly, jaundice, and anorexia. Fever is typically modest (<38.3°C). There are several characteristic laboratory abnormalities in alcoholic hepatitis. The most typical is serum aminotransferase elevations to less than 500 international units/L with a disproportionate elevation of aspartate aminotransferase (serum glutamic oxaloacetic transaminase) compared with alanine aminotransferase (serum glutamic pyruvic transaminase); the ratio is usually greater than 2.0, a value that is rarely seen in other forms of liver disease.

- **Other** — A number of other noninfectious disorders may present as an FUO:
- ●Venous thrombosis and thromboembolism, although more common presentations include dyspnea, pleuritic pain, cough, and hemoptysis.
- ●Hematoma (eg, from trauma, rupture of an aortic aneurysm, or spontaneously in an anticoagulated patient) with subsequent inflammation. The hip, pelvis, and retroperitoneum can hide a substantial amount of blood.
- ●Hyperthyroidism and subacute thyroiditis occasionally cause FUO, although these conditions most frequently are diagnosed clinically.
- ●Other endocrine causes of fever include pheochromocytoma and adrenal insufficiency .
- ●Hereditary periodic fever syndromes, such as familial Mediterranean fever, tumor necrosis factor receptor-1–associated periodic syndrome (also called TRAPS), hyper-IgD syndrome, Muckle-Wells syndrome, and familial cold autoinflammatory syndrome .

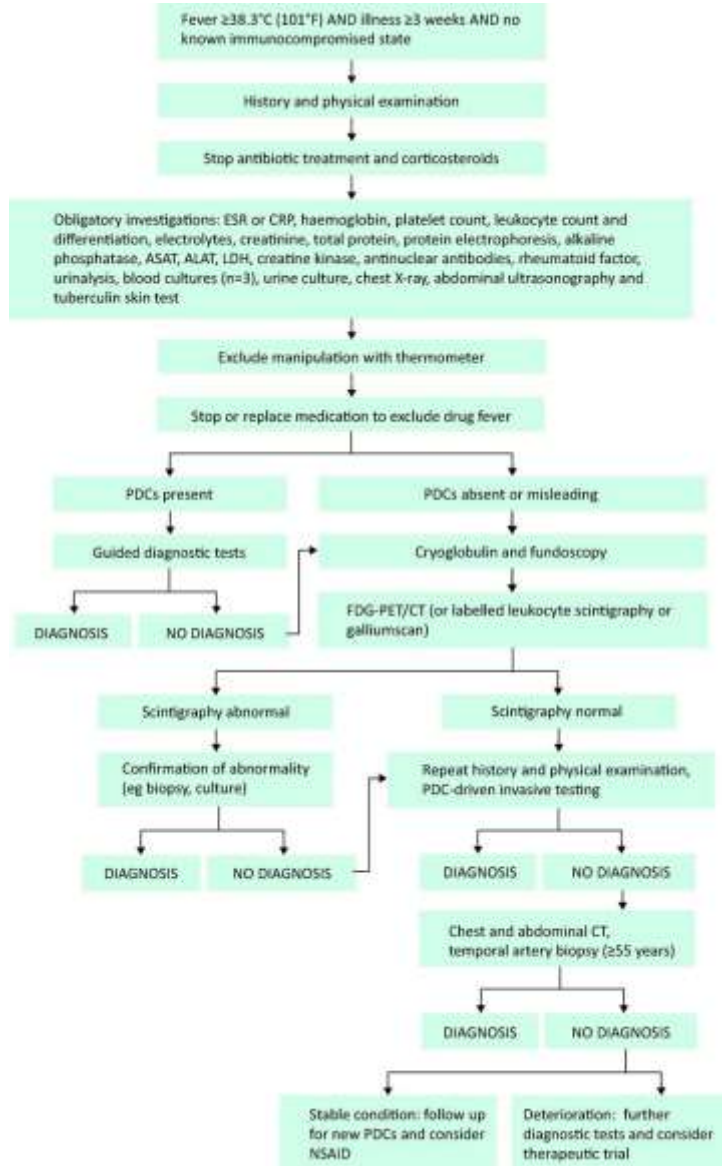
EPIDEMIOLOGY

- **Changes over time** — Scientific and technologic advances have greatly refined and expedited the differential diagnosis and therapy of FUO .
- ●The fraction of undiagnosed FUOs dropped from over 75 percent in the 1930s to less than 10 percent in the 1950s. Since then, the fraction of FUOs that go undiagnosed has steadily increased.
- ●Extrapulmonary tuberculosis, solid tumors, and abdominal abscesses are now less prevalent causes due to earlier diagnosis by radiologic imaging, particularly computed tomography, and minimally invasive biopsies.
- ●Infective endocarditis, once a frequent cause of FUO, has become a less common cause with improved techniques for the isolation of organisms. In the current era, when endocarditis is ultimately diagnosed in a patient with FUO, it is more likely to be culture negative or caused by difficult-to-isolate organisms, such as *Bartonella quintana*.

- True FUOs are uncommon. This was illustrated in a report from the Netherlands in which only 73 patients were identified between December 2003 and July 2005 at a 950-bed academic referral hospital and five community hospitals comprising 2800 hospital beds. The authors excluded immunocompromised patients, such as those with AIDS, hypogammaglobulinemia, granulocytopenia, and glucocorticoid therapy. The following distribution of causes was noted:
- ●Systemic rheumatic disease (eg, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica) – 22 percent
- ●Infection – 16 percent
- ●Malignancy – 7 percent
- ●Miscellaneous – 4 percent
- ●No diagnosis – 51 percent

- **Geography** — Infectious causes of prolonged fever in resource-limited countries include tuberculosis, typhoid, amebic liver abscesses, and AIDS. Ease of travel has the potential to bring back to the United States and other resource-rich countries more geographically restricted illnesses that may not be familiar to clinicians, such as malaria, brucellosis, kala azar, filariasis, schistosomiasis, African tick bite fever, relapsing fever, Q fever, dengue virus, chikungunya virus, Zika virus, or Lassa fever .
- Illnesses contracted abroad may have incubation periods that extend for months; some infections remain latent for years and may therefore present as fevers remote from the time of travel. Individuals traveling may also become infected with organisms to which local residents are not vulnerable because of pre-existing immunity.

- **Subpopulations** — Different entities figure in the etiology of FUO based upon features of the population being studied.
- **Age** — The causes of FUO vary dramatically with age. In a series of 100 children with FUO, for example, one-third were self-limited undefined viral syndromes . In contrast, multisystem diseases such as systemic rheumatic diseases (including polymyalgia rheumatica, giant cell arteritis, and other vasculitides) and sarcoidosis accounted for 31 percent of cases in a review of patients with FUO over the age of 65 . Infections accounted for 25 percent and neoplasms 12 percent of cases in this report.
- **AIDS**
- **Neutropenia**


Fever ≥38.3°C (101°F) AND illness ≥3 weeks AND no known immunocompromised state
History and physical examination
Stop antibiotic treatment and corticosteroids
Obligatory investigations: ESR or CRP, haemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, ASAT, ALAT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n=3), urine culture, chest X-ray, abdominal ultrasonography and tuberculin skin test
Exclude manipulation with thermometer
Stop or replace medication to exclude drug fever
PDCs present
PDCs absent or misleading
Guided diagnostic tests
Cryoglobulin and fundoscopy
DIAGNOSIS
NO DIAGNOSIS
FDG-PET/CT (or labelled leukocyte scintigraphy or galliumscan)
Scintigraphy abnormal
Scintigraphy normal
Confirmation of abnormality (eg biopsy, culture)
Repeat history and physical examination, PDC-driven invasive testing
DIAGNOSIS
NO DIAGNOSIS
DIAGNOSIS
NO DIAGNOSIS
Chest and abdominal CT, temporal artery biopsy (≥55 years)
DIAGNOSIS
NO DIAGNOSIS
Stable condition: follow up for new PDCs and consider NSAID
Deterioration: further diagnostic tests and consider therapeutic trial

DIAGNOSTIC APPROACH

- The most critical feature of the evaluation of a patient with FUO is to take a careful history and to reassess the patient frequently. It is important to look for uncommon presentations of common diseases and to perform a detailed physical examination.
- **History and physical examination** — The history and physical examination, like laboratory tests, have the potential to generate valuable diagnostic clues in patients with FUO. The art of diagnosis is one of discrimination, as the clinician must determine which data to glean and which clues to pursue.
- A thorough history should include the following information:
- ●Travel
- ●Animal exposure (eg, pets, occupational, living on a farm)
- ●Immunosuppression (with the degree noted)
- ●Drug and toxin history, including antimicrobials
- ●Localizing symptoms

- Subtle findings may be elicited through a careful history. Examples include subtle changes in behavior or cognition consistent with granulomatous meningitis, jaw claudication consistent with giant cell arteritis, tooth sensitivity to cold or gum tenderness consistent with dental abscesses, and nocturia consistent with prostatitis. Revisiting the history on several occasions may provide new clues in difficult cases.
- The degree of fever, nature of the fever curve, apparent toxicity, and response to antipyretics has **not** been found to provide enough specificity to guide the diagnosis of FUO . Fever may be attenuated in older patients and moderated by use of steroids and nonsteroidal anti-inflammatory drugs. However, the course of the fever curve may be helpful in determining whether the disease is escalating or waning.

- **Initial laboratory testing in all patients** — In addition to basic testing that establishes an FUO , we typically perform the following minimum diagnostic evaluation for patients who have true FUO. We individualize other laboratory tests based on clinical and historical findings.
- ●Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) – Measurement of the ESR seems to have its greatest use in establishing a serious underlying cause of FUO. In a review of 263 patients with FUO who had ESR elevations above 100 mm/hour, 58 percent had malignancy (most commonly lymphoma, myeloma, or metastatic colon or breast cancer) and 25 percent had infection (eg, endocarditis) or systemic rheumatic diseases (eg, rheumatoid arthritis or giant cell arteritis) . However, other causes of FUO, such as drug hypersensitivity reactions, thrombophlebitis, and renal disease, particularly nephrotic syndrome, may be associated with a very high ESR in the absence of infection or malignancy. A normal ESR or CRP also suggests that a significant inflammatory process, of whatever origin, is absent; however, there are exceptions. As an example, some patients with giant cell arteritis have a normal ESR.
- ●Serum lactate dehydrogenase
- ●Tuberculin skin test or interferon-gamma release assay
- ●HIV immunoassay and HIV viral load for patients at high risk
- ●Three routine blood cultures drawn from different sites over a period of at least several hours without administering antibiotics, if not already performed

- ●Rheumatoid factor
- ●Creatine phosphokinase
- ●Heterophile antibody test in children and young adults
- ●Antinuclear antibodies
- ●Serum protein electrophoresis
- ●Computed tomography (CT) scan of the chest and abdomen. Details regarding this test are found below
- Procalcitonin, a serum biomarker that is elevated with certain bacterial infections, has no clear role in distinguishing between bacterial infections and other causes of FUO, and we do not recommend checking it as part of the FUO evaluation.

- **Imaging studies** — Most providers perform some type of imaging early during the diagnostic work-up of FUO. Various radiologic imaging studies have been studied for their ability to determine the cause of FUO. In general, studies suggest that radiographic imaging modalities are hampered by high rates of false-positive and false-negative results.

- CT scanning of the abdomen has nearly replaced exploratory laparotomy and other radiographic tests in the search for occult abscesses or hematomas in patients with FUO. The finding of abdominal lymphadenopathy can be a clue to lymphoma or a granulomatous process. The usefulness of CT has resulted in this examination being used in nearly all patients with FUO. While magnetic resonance imaging scan can be more sensitive in certain settings (eg, the diagnosis of spinal epidural abscess), it is rarely required in the initial evaluation of FUO.
- For similar reasons, CT scanning of the chest is invaluable in the identification of small nodules (indicative of fungal, mycobacterial, or nocardial infection or malignancy). The identification of hilar or mediastinal adenopathy may prompt biopsy by mediastinoscopy, providing a diagnosis of lymphoma, histoplasmosis, or sarcoidosis.

- **Nuclear medicine testing in selected cases** — Nuclear medicine testing is more controversial than CT for the diagnosis of FUO. All nuclear medicine tests used for FUO image the whole body, but none can establish a definitive diagnosis. In many cases, these studies are used to localize a site for more specific evaluation (eg, biopsy or further imaging). In select cases, nuclear medicine findings can be suggestive enough to warrant treatment (eg, arteritis, pulmonary embolism, some tumors).
- We generally reserve nuclear medicine imaging for cases in which the initial evaluation (including abdominal and chest CT) remains negative. Two types of nuclear medicine tests are used for FUO workups: labeled white blood cell (WBC) or gallium scans, and F-fluorodeoxyglucose positron emission tomography (FDG-PET).

- **Additional testing for specific circumstances** — When the history, examination, or imaging suggests a possible source, specific testing should be performed. Examples include:
- ●Subtle central nervous system symptoms or signs should prompt a lumbar puncture and imaging of the head and/or spine.
- ●In the United States, a travel history to the Midwest or the deserts of the West should raise the question of a fungal process like histoplasmosis or coccidioidomycosis, respectively. Testing for the suspected fungal pathogen in individuals who have resided in an endemic area can be useful.
- ●Individuals who have recently visited or resided in a malaria-endemic region should have blood sent for a thick and thin smear.
- ●A history of trauma, adjacent infection or intravenous drug use may suggest thrombophlebitis of the legs, arms, or pelvic vessels. Venous duplex imaging can be diagnostic. Fever usually responds to anticoagulation within several days.
- ●Molecular tests include next-generation sequencing, broad-range or multiplex polymerase chain reaction (PCR) assays, D1-D2 region assays, and others. We suggest reserving these types of tests for patients in whom FUO is persistent and diagnosis is elusive despite thorough work-up.

- **Biopsy** — Biopsy is a critical modality in the directed (as opposed to screening) evaluation of FUO.
- We suggest performing a biopsy when the clinical data support a diagnosis that can be confirmed from a tissue sample, especially when the risks are low (e.g., skin biopsy). Blind biopsies rarely yield helpful results.
- However, like all diagnostic tests, biopsies can have false-negative or false-positive results. For example, false-negatives can occur due to inadvertently sampling an unaffected site, and false-positives can occur when a concurrent condition is detected that is not causing the FUO.

Treatment

- When all previously described investigations do not lead to the diagnosis, further investigations should only be carried out when the patient deteriorates, or when new PDCs are identified by repeated history taking and physical examination. In stable patients without a diagnosis, non-steroidal anti-inflammatory drugs can be used as antipyretics.
- When no cause for the fever is found and the patient deteriorates despite extensive investigation, a drug trial should be considered. Corticosteroids are an option, but they should not be prescribed too early, as important diagnostic clues can be altered or even disappear with steroid treatment, thereby delaying diagnosis and targeted specific therapy. In patients with a suspected autoinflammatory disorder the interleukin-1 receptor antagonist, anakinra, can be tried. Remission of symptoms is expected within 24–48 hours. If anakinra is ineffective after two weeks of treatment, a beneficial effect should not be expected and the drug should be stopped.

Prognosis

- The overall prognosis of FUO is determined by the underlying disease. In patients in whom no cause of FUO can be established, prognosis is generally good and mortality is low. Up to 75% of patients experience spontaneous remission of fever, although this may take a long time. Treatment with NSAIDs or corticosteroids increases this proportion even further.

SUMMARY AND RECOMMENDATIONS

- ●**Definition** – Fever of unknown origin (FUO) is defined as fever higher than 38.3ºC on several occasions lasting for at least three (some use two) weeks without an established etiology despite intensive evaluation and diagnostic testing.
- ●**Etiology** – Three general categories account for the majority of FUO cases: infections, malignancies, and systemic rheumatic diseases.
- ●**Factors that affect etiology** – The likelihood of a specific etiology varies substantially based on a patient's age, exposures, and immune status.
- ●**Work-up** – The most important aspects of the evaluation of a patient with FUO are to take a meticulous history, perform a detailed physical examination, and reassess the patient frequently.
- •**Diagnostic tests** – We suggest the following minimum diagnostic evaluation: blood cultures, erythrocyte sedimentation rate or C-reactive protein, serum lactate dehydrogenase, HIV antibody test and viral load, rheumatoid factor, heterophile antibody test for mononucleosis, creatine phosphokinase, antinuclear antibodies, tuberculin skin test or interferon-gamma release assay, serum protein electrophoresis, and computed tomography scan of abdomen and chest.
- •**Role of biopsy** – We suggest performing a biopsy when the clinical data support a diagnosis that can be confirmed from a tissue sample, especially when the risks are low (eg, skin biopsy).
- ●**Outcome** – The diagnostic evaluation may fail to identify an etiology in as many as 30 to 50 percent of patients. Most adults who remain undiagnosed have a good prognosis.