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Fever of unknown origin in adults: Evaluation and management

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INTRODUCTION

Clinicians commonly refer to a febrile illness without an initially obvious etiology as fever of unknown origin (FUO). However, 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.

Large case series of FUO have been collected over a number of decades; these facilitate an approach to patients with FUO and provide an understanding of the changing patterns of FUO with time and newer diagnostic techniques.

The definitions and special populations with FUO, as well as the diagnostic approach to the adult with FUO, are reviewed here. Specific discussions of the common and uncommon entities causing FUO and the approach to children with FUO are presented separately. (See "Fever of unknown origin in adults: Etiologies" and "Fever of unknown origin in children: Evaluation".)

DEFINITIONS AND CATEGORIES OF FUO

From the perspective of a practicing clinician, an overarching definition of FUO is fever persisting longer than typical self-limiting conditions (eg, common viral illnesses) in the absence of an identifiable cause despite a reasonable evaluation by an experienced clinician.

Many clinical researchers have attempted to more precisely define FUO, but development of a clear definition has been elusive. Proposed definitions for FUO typically have three components:

- **Definition of fever** – To define fever, one must first understand normal temperature variation. In adults, the mean normal body temperature is 36.7˚C (97.9˚F), and temperature fluctuates based on the time of day. The highest temperatures (up to 38˚C [100.4˚F]) occur in the late afternoon/early evening. Lower baseline temperatures (down to 35.3˚C [95.5˚F]) are associated with older age and lower body mass index. (See "Pathophysiology and treatment of fever in adults", section on 'Normal body temperature'.)

  Most FUO studies have defined fever as a temperature >38.3˚C (100.9˚F), although definitions range from 38.0˚C (100.4˚F) to 38.5˚C (101.3˚F) [1-11]. Because the peak normal temperature in well individuals is 38.0˚C, experts have more recently proposed a cut-off temperature for FUO of >38.0˚C (100.4˚F) instead of >38.3˚C (100.9˚F) [11].

- **Minimum duration of fever** – A minimum of three weeks of unexplained febrile episodes is typically required to meet most proposed definitions of FUO.

- **Minimum diagnostic testing** – Most definitions require that certain diagnostic tests be performed before a fever can be labeled to have an "unknown origin." The necessary tests vary but typically include basic laboratory tests (eg, complete blood count, urinalysis) as well as certain radiographic imaging.

FUOs are divided into four categories (table 1) [12-18]:

Classic FUO — In most studies, classic FUO is defined as a temperature >38.3˚C (100.9˚F) recorded on several occasions for >3 weeks, despite an appropriate initial inpatient or outpatient evaluation (table 1) [11].

From a clinical perspective, we often manage our patients as if they have FUO even if they don't meet the above parameters. For instance, we may consider a fever to be any temperature >38.0˚C (100.4˚F) or require a duration of two weeks instead of three. Additionally, some patients may meet the definition of FUO except they may not have had a basic workup; in such cases, we often combine the basic workup necessary to confirm the diagnosis of FUO with

components of the initial workup performed on patients with confirmed FUO. Ultimately, clinical judgment is necessary to decide whether to diagnose and pursue a workup for classic FUO.

Health care-associated FUO — Patients undergoing or recently exposed to health care are at risk for specific infectious and noninfectious causes of fever. In such patients, FUO is often divided based on whether the patient is hospitalized in the ICU, hospitalized outside the ICU, or recently underwent surgery (table 1). (See "Fever in the intensive care unit" and "Fever in the surgical patient".)

FUO in immunocompromised patients — Immunocompromised patients are at risk for a broad range of opportunistic infections in addition to more common conditions (table 1).

Defining immunocompromise in patients with FUO is challenging. Some experts have proposed the following definition:

- Neutropenia (absolute neutrophil count <500 cells/microL for at least one week within three months prior to start of fever) (see "Overview of neutropenic fever syndromes")
- Use of immunosuppressive drugs for solid organ or hematologic stem cell transplant (see "Infection in the solid organ transplant recipient" and "Overview of infections following hematopoietic cell transplantation")
- Known hypogammaglobulinemia (see "Clinical manifestations, epidemiology, and diagnosis of common variable immunodeficiency in adults" and "Secondary immunodeficiency induced by biologic therapies")
- Use of 10 mg prednisone or equivalent for ≥2 weeks in the three months prior to fever (see "Major adverse effects of systemic glucocorticoids")
- Uncontrolled human immunodeficiency virus (HIV) infection or CD4 <200 cells/mL (see "Overview of prevention of opportunistic infections in patients with HIV")
- Use of biologic therapies (eg, anti-tumor necrosis factor or monoclonal antibody) (see "Evaluation and prevention of infections associated with biologic agents and JAK inhibitors in adults")

Travel-associated FUO — Patients who recently traveled to foreign countries may return to their home country with unexplained febrile illnesses that can be unfamiliar to clinicians in the patient's home country (table 1). (See "Evaluation of fever in the returning traveler".)

INITIAL EVALUATION AND MANAGEMENT

Regardless of how a clinician defines FUO, a methodical approach is recommended.

- **Pace of evaluation** – Because patients diagnosed with classic FUO have had prolonged fever, many can undergo an initial or sequential outpatient evaluations instead of being hospitalized.

  However, for patients who are severely ill or thought to be at risk for a life-threatening condition, hospitalization is appropriate to hasten diagnostic testing or provide rapid empiric treatment.

- **Protocol-driven evaluation** – Some experts have advocated for the use of a structured protocol-based approach to testing (eg, having a minimum set of studies performed for all patients with FUO), whereas others suggest avoiding a routine battery of tests. A systematic review and meta-analysis found insufficient evidence to support one approach over the other [19].

  We typically use a protocol-based approach and supplement the tests in the protocol with additional tests if the patient's history and examination suggest a specific diagnosis.

Obtaining a history — The importance of obtaining a detailed history cannot be overstated in the evaluation of FUO. From our experience, delays in determining the cause of FUO can often be traced to initial gaps in the patient's history.

If possible, we also obtain a collateral history from the patient's partner or family member. They may recall information that the patient withheld or forgot. Additionally, the partner's history may be relevant (eg, if the partner works in an abattoir with animals infected with Q fever and brings home work clothes).

History of present illness — The history of present illness should focus on the fever itself as well as any associated symptoms. It is often useful to focus on the temporal relationship of these associated symptoms. For example, a patient who develops jaundice or joint swelling and then fever is likely to have a different final diagnosis than a patient who develops fever and then jaundice or joint symptoms.

Fever history — Information to acquire about the fever includes the date of the first episode of fever, the maximum daily temperatures recorded by the patient, and the duration and frequency of febrile episodes. (See 'Classic FUO' above.)

- **Definition of fever** – It is important to recognize that temperature variation is normal and that experts differ on the temperature threshold for fever (the traditional definition is >38.3˚C [100.9˚F] compared with more recent proposed definition of >38.0˚C [100.4˚]F).

(See 'Definitions and categories of fuo' above and "Pathophysiology and treatment of fever in adults", section on 'Individual daily variation'.)

- **Fever patterns** – Historically, fever patterns have been used to attempt to narrow the differential diagnosis of FUO. However, specific fever patterns have not been proven to be sensitive or specific enough to narrow the differential, as discussed separately [18]. (See "Pathophysiology and treatment of fever in adults", section on 'Deciding whether to treat'.)

  Fever patterns mentioned in the literature include tertian and quartan fever patterns (ie, fevers every 48 hours or 72 hours, respectively) associated with malaria and Pel-Ebstein patterns (fevers that cyclically increase then decrease over a period of one to two weeks) associated with Hodgkin's lymphoma.

- **Method of temperature measurement** – It is also important to determine how a patient obtains their temperature and whether there are witnesses at home who can corroborate the results. Some patients assume they have a fever because of subjective symptoms (eg, chills, sweats); these patients should be advised to perform actual temperature measurements with a thermometer before further workup is performed.

  Although rectal temperature is the most accurate, oral or tympanic membrane thermometers are usually adequate However, the quality of commercially available tympanic membrane (TM) thermometers varies substantially. Axillary and infrared contact and noncontact forehead thermometers are not recommended due to significant variations in results. Further details regarding temperature measurement are available separately. (See "Fever in infants and children: Pathophysiology and management", section on 'Site and method of measurement' and "Pathophysiology and treatment of fever in adults", section on 'Methods of measurement'.)

Associated symptoms — Additional manifestations of illness may occur during febrile episodes or may have no clear relationship to the fevers.

- Symptoms associated with febrile episodes include:

  - Rigors – Shaking chills (ie, rigors) are often associated with infectious etiologies, especially bacteremia, but can also be associated with reactions to drugs, including biologic agents and chimeric antigen receptor (CAR)-T cell therapy and other causes. (See "Cytokine release syndrome (CRS)", section on 'Clinical manifestations' and "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy", section on 'Signs and symptoms'.)

- Diaphoresis, fatigue, and malaise – These nonspecific symptoms are commonly associated with fevers of any etiology and may also be present in some patients who do not truly have a fever.

- Evanescent rash during fever – A rash that appears on the trunk and/or extremities during fever and disappear as fever resolves may be indicative of adult-onset Still's disease. (See "Clinical manifestations and diagnosis of adult-onset Still's disease", section on 'Rash'.)

- Additional symptoms – A complete review of systems should be obtained on initial presentation. Specific symptoms can help to focus the workup of FUO, especially when grouped together. For instance, the combination of fever, oral ulcers, and rash should prompt consideration of acute HIV syndrome (see "Acute and early HIV infection: Clinical manifestations and diagnosis", section on 'Clinical features'). As explained above, the sequence of the onset of additional symptoms can be diagnostically useful.

  An extensive list of symptoms associated with FUO and their potential causes can be found in the table (table 2).

Past medical history — A thorough medical history should be obtained because many medical diseases are risk factors for conditions that are known to cause FUO. Examples include the following:

- Valvular or congenital heart disease, or prosthetic heart valve – These conditions are risk factors for infectious endocarditis. (See "Native valve endocarditis: Epidemiology, risk factors, and microbiology", section on 'Risk factors'.)

- Past exposure to or history of tuberculosis, BCG vaccination, or positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) test – alters baseline risk for tuberculosis.

- History of orthopedic or other metal implants – These can be sites of insidious infection.

- Immunocompromising condition – Patients with a significant immunocompromising condition are categorized and managed differently than patients with classic FUO. (See 'FUO in immunocompromised patients' above and "Overview of neutropenic fever syndromes" and "Infection in the solid organ transplant recipient" and "Overview of prevention of opportunistic infections in patients with HIV".)

- Silicosis of the lungs – predisposes to tuberculosis. (See "Epidemiology of tuberculosis", section on 'Risk factors'.)

- History of malignancy – raises concern for recurrent or metastatic malignancy.
- Prior sexually transmitted infections (STIs) – Increases risk for recurrent or new STIs.
- Injection drug use – increases risk for numerous infections, including endocarditis, tuberculosis, viral hepatitis, and HIV.
- Von Hippel-Lindau disease- predisposes to renal cell carcinoma.

Medications — Many medications can cause fever. A medication history should include prescription and over-the-counter medications, cannabis, herbal supplements, home remedies, and anything else the patient is taking for medical purposes.

We often ask the patient to bring their medications to clinic so we can ensure accurate and complete information.

Detailed discussion of drug fever is found separately. (See "Drug fever".)

Family history — Fever-inducing illnesses may be genetically inherited or have familial predilections without clear genetic lineage.

For example, multiple genes have been identified for Familial Mediterranean fever, as discussed separately. (See "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis", section on 'Genetics'.)

Conditions such as systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease are more likely to occur in individuals whose family members have had the same diagnosis.

Social history, including exposures — Social history is of paramount importance in evaluating patients with classic FUO. There are numerous components of a thorough social history, and details relayed in the social history often alter the clinical evaluation.

- **Close contacts and their illnesses** – Determining who a patient lives with provides information about their level of support at home. If any close contacts have had febrile illnesses, elucidating the cause of the illness may be of value. Often, viral infections (eg, Epstein-Barr virus) spread among close contacts.
- **Residential and travel history** – Patients should be queried about where they were born, countries where they have lived or spent prolonged periods of time, and any foreign travel. Additionally, patients should be asked if they've ever spent significant time in prisons, jails, or congregate living facilities.

An array of different tropical and nontropical infections are more common in specific regions of the world. An understanding of conditions endemic to areas where the patient resides or has visited is necessary to pursue appropriate workup. (See "Evaluation of fever in the returning traveler" and "Approach to illness associated with travel to South Asia" and "Approach to illness associated with travel to Southeast Asia" and "Approach to illness associated with travel to East Asia" and "Approach to illness associated with travel to West Africa" and "Approach to illness associated with travel to Latin America and the Caribbean".)

Infections contracted abroad may have incubation periods that extend for months; some infections remain latent for years (eg, tuberculosis, meliodosis, endemic mycotic diseases) and may therefore present as fevers remote from the time of travel. For this reason, understanding where patients lived in the past is of value. (See "Pulmonary tuberculosis: Clinical manifestations and complications", section on 'Reactivation (postprimary) tuberculosis'.)

- **Occupational history, hobbies, and sports** – A patient's work history can reveal exposures that predispose to certain conditions. For example, dentists and other health care personnel may be at increased risk for HIV and other bloodborne pathogens; individuals who work with certain chemicals are at increased risk of renal cell carcinoma; and microbiology laboratory workers are at risk for numerous pathogens. (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Occupational exposure'.)

  Patients should be asked about their hobbies and how they spend their free time. Some cases of FUO can be traced to hobbies that wouldn't otherwise be identified without specific questioning.

- **Outdoor exposures** – The outdoor environment can predispose to certain infections. Examples include soil (histoplasmosis, blastomycosis, coccidioidomycosis, leptospirosis), caves (histoplasmosis), and natural or flood waters (typhoid/enteric fever, leptospirosis, schistosomiasis, melioidosis). See separate UpToDate disease-specific topics for details.

- **Animal exposures** – Animals are associated with numerous infections. Animal exposures include pets (cat-scratch disease), livestock (brucellosis, Q fever), and wild animals (tularemia from rabbits), as discussed separately. (See "Zoonoses: Animals other than dogs and cats" and "Zoonoses: Dogs" and "Zoonoses: Cats".)

- **Insect exposures** – Insects act as vectors to transmit certain infections that can cause chronic fever, including mosquitoes (eg, malaria), lice, fleas, mites, and ticks. (See "Malaria:

Epidemiology, prevention, and control", section on 'Transmission' and "Evaluation of fever in the returning traveler", section on 'Arthropod bites'.)

- **Food and drink habits** – Infections transmitted by contaminated food and water (eg, typhoid/enteric fever) are more likely to occur in resource-limited countries. Unpasteurized dairy products (eg, milk and cheese) can cause brucellosis and other infections. (See "Enteric (typhoid and paratyphoid) fever: Epidemiology, clinical manifestations, and diagnosis", section on 'Risk factors' and "Brucellosis: Epidemiology, microbiology, clinical manifestations, and diagnosis", section on 'Transmission'.)

- **Smoking and drug use history** – Smoking cigarettes is a risk factor for numerous malignancies. Drug use by any route (injecting, smoking, inhaling, snorting, skin popping) can lead to numerous infectious and noninfectious febrile illnesses, including endocarditis, acute HIV, hepatitis B and C, interstitial lung disease, sinusitis, drug-induced vasculitis, and others.

- **Sexual history** – Sexual history should include recent and remote sexual activity, number of sexual contacts, gender, and types of sexual activity. Sexually transmitted syndromes that can manifest as FUO include acute HIV, disseminated gonococcus, and pelvic inflammatory disease. (See "Acute and early HIV infection: Pathogenesis and epidemiology", section on 'Epidemiology' and "Pelvic inflammatory disease: Pathogenesis, microbiology, and risk factors", section on 'Risk factors'.)

- **Recent healthcare exposure** – Health care exposure, including dental and outpatient care, and medical care in other countries is associated with a number of causes of FUO, as discussed separately. (See 'Health care-associated FUO' above and "Fever in the intensive care unit" and "Fever in the surgical patient" and "Carbapenem-resistant *E. coli*, *K. pneumoniae*, and other Enterobacterales (CRE)", section on 'Classifications and geographic distribution' and "Aseptic meningitis in adults", section on 'Fusarium outbreaks'.)

Physical examination — A thorough physical examination is of paramount importance in patients with classic FUO.

Every organ system should be evaluated, and the results of the physical examination should be used to help guide further workup. There may be aspects of the examination that are necessary in patients with FUO that may not be part of a clinician's usual practice.

Thorough physical examination should include the following (table 3). Specific exam findings and their associated causes can be found in the table (table 2).

- Temporal arteries
- Ophthalmologic examination (including conjunctivae, fundoscopy)
- Oral cavity (palate, teeth, gums)
- Thyroid
- Lymph nodes (neck, supraclavicular, axillae, groin)
- Lungs
- Heart
- Abdomen (including liver and spleen size, rectal and prostate exam)
- Genitalia (including testes/epididymis and gynecologic pelvic exam in woman with pelvic symptoms)
- Neurologic examination (including cranial nerves and cognition)
- Joints and spine
- Skin and nails (including wounds under dressings and casts)

Initial diagnostic testing

Basic tests for all patients — We obtain the tests listed below in all adults with classic FUO (table 3). Additional tests are indicated if the history or examination suggest a specific diagnosis or diagnoses (table 2). (See 'Targeted testing' below.)

We base our initial testing protocol on the most common causes of classic FUO in our practice area (ie, Australia and southeastern United States); clinicians in other locations may alter their initial testing based on local epidemiology.

- Complete blood count with differential and peripheral smear.
- Complete metabolic panel, including calcium.
- Liver biochemical tests (eg, aminotransferases, alkaline phosphatase, bilirubin).
- Blood cultures (two sets) obtained from two separate venous sites prior to administration of any antibiotics; we ask the microbiology laboratory to incubate the cultures for at least five days.
- Urinalysis with reflex to urine culture.
- HIV antigen/antibody testing with reflex confirmatory testing. If we think the risk of HIV is exceptionally low, we may consider not obtaining an HIV test as part of the initial workup. If acute HIV syndrome is suspected, we also obtain an HIV viral load. Details regarding HIV testing can be found separately. (See "Screening and diagnostic testing for HIV infection".)
- Antinuclear antibodies.
- Rheumatoid factor.
- Heterophile antibody test (eg, Monospot test) or Epstein-Barr virus antibody tests in young adults. If associated mononucleosis is strongly suspected in a patient with a negative

heterophile antibody test, Epstein-Barr virus antibody tests should be performed; for such patients, we would also include tests for other causes of mononucleosis-syndrome (HIV testing, cytomegalovirus immunoglobulin (Ig)G and IgM or viral load, and toxoplasma IgM and IgG).

- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). We do not routinely obtain procalcitonin levels; the utility of this test in adults with FUO is unclear.
- Ferritin.
- Thick and thin blood smears for malaria. In areas where malaria is endemic, this test should be performed as part of initial testing. Even in areas where malaria is not endemic, testing should be considered if clinical features or laboratory tests are consistent with the illness (eg, new anemia or thrombocytopenia). In 2023 in the United States, the first cases of locally acquired malaria since 2003 were identified, specifically in the states of Florida, Texas, Arkansas, and Maryland [20-23].

- CT of the chest, abdomen, and pelvis with contrast.

These tests provide clues to some of the most common causes of classic FUO as well as serious illnesses for which prompt diagnosis improves outcome.

Additional testing — We obtain additional targeted testing if the history and physical examination suggest a specific etiology or etiologies. The table lists specific symptoms and physical exam findings that are suggestive of certain illnesses (table 2).

Further discussion of targeted testing is found below. (See 'Targeted testing' below.)

Initial management — As described above, the patient's clinical presentation determine the site and pace of initial management and evaluation. (See 'Initial evaluation and management' above.)

Most patients with classic FUO are managed as outpatients. In the outpatient setting, our initial approach is as follows:

Fever diary — We advise all patients with prolonged unexplained fevers to maintain a fever diary. Information recorded in the diary include the date, time, height, and duration of fevers as well the heart rate during fevers. The method of assessment (eg, mouth versus other sites of measurement), associated symptoms, and timing and dosage of any antipyretic medications should also be recorded. In patients who have asymptomatic fevers, we advise recording the temperature three to four times a day (morning, noon, late afternoon/early evening, and bedtime).

Temperature should be taken orally or by TM with same device (see 'Fever history' above). In some cases, confirming the patient's device is accurate by comparing to clinic thermometer may be helpful.

Although nonspecific, fever curves may be suggestive of certain diseases, as described above (see 'Fever history' above). In addition, temperature-pulse dissociation (ie, relative bradycardia; when the heart rate does not increase at the rate expected with fever) may be a clue for conditions such as enteric fever (eg, typhoid fever), brucellosis, drug fever, and factitious fever. (See "Pathophysiology and treatment of fever in adults", section on 'Deciding whether to treat'.)

Discontinue nonessential medications — Nonessential medications should be discontinued, especially new medications or those known to cause fevers. For patients on multiple fever-causing medications, serial discontinuation may help to identify the offending drug. Resolution of fever within two half-lives of the drug (usually within three to four days) supports the diagnosis of drug fever. (See "Drug fever".)

Deciding whether to use antipyretics — During periods when the patient is afebrile, we advise **not** taking antipyretics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]) because they can mask important differentiating features of the illness as well as eliminate the ability to monitor fever patterns. Once fever occurs, we advise patients to continue to avoid antipyretics unless they are uncomfortable or have risk factors for complications from fever (eg, seizure, cardiac disease). (See "Pathophysiology and treatment of fever in adults", section on 'Deciding whether to treat' and "Pathophysiology and treatment of fever in adults", section on 'Selection of antipyretic'.)

Limited role of empiric antibiotics and glucocorticoids — We generally **avoid** empiric antibiotics, and we do not administer empiric glucocorticoids to patients during their initial evaluation.

- **Empiric antibiotics** – For patients suspected of having a potentially life-threatening infection, empiric antibiotics should be administered that target the suspected pathogen while test results are pending. Otherwise, we avoid antibiotics because they can mask or delay diagnosis of serious infections (eg, endocarditis, meningitis) and interfere with isolation of an organism from cultures. To optimize culture results, blood cultures, and urine cultures if indicated, should be obtained prior to starting antibiotics.

- **Empiric glucocorticoids** – For patients strongly suspected of having giant-cell arteritis, we begin corticosteroids immediately to prevent complications, such as permanent visual loss or stroke. Planned biopsy should not delay the start of corticosteroids; biopsy results are

not altered by corticosteroids, at least during the first month of therapy. (See "Diagnosis of giant cell arteritis", section on 'Temporal artery biopsy'.)

For other patients, we do not administer glucocorticoids unless the patient is severely ill and glucocorticoids would be expected to improve the patient's condition. Glucocorticoids can worsen infections and mask malignancies, including altering biopsy results for malignancies.

SUBSEQUENT EVALUATION AND MANAGEMENT

If fevers resolve spontaneously — Often, patients fevers resolve with no identified etiology. In such patients, particularly when other associated symptoms also resolve, we perform no further workup and advise patients to return for medical care if fevers or other symptoms return. For patients on antipyretics, the antipyretics must be discontinued to confirm resolution of fever.

Persistent fevers — Patients with persistent FUO should undergo serial evaluations and sometimes sequential testing. In the outpatient setting, we typically examine our patients once weekly for the first few weeks. At follow-up visits, repeat history and examination are performed; the patient's fever diary is reviewed; and prior laboratory and imaging results are discussed. During the history, patients sometimes recall additional information that was not elicited during the initial history. (See 'Obtaining a history' above and 'Physical examination' above.)

Targeted testing — Results of the history, examination, and laboratory and imaging results provide diagnostic clues that should be analyzed holistically to find potential unifying diagnoses. The table lists specific symptoms and physical exam findings that are suggestive of certain illnesses (table 2).

Example tests that can be pursued if a specific illness is suspected include the following:

- **Mononucleosis** – In patients with compatible symptoms and sick contacts, mononucleosis remains a consideration even if the heterophile test is negative. Additional tests for these patients include Epstein-Barr serology, HIV viral load, cytomegalovirus serology or polymerase chain reaction (PCR), and toxoplasma serology. (See "Infectious mononucleosis", section on 'Diagnosis'.)

- **Infective endocarditis** – In patients with new or changed heart murmur or unexplained bacteremia, endocarditis is a consideration. Echocardiogram and blood cultures are the

mainstay of diagnosis.

- **Tuberculosis** – Tests in patients with a compatible syndrome or risk factors for tuberculosis should include sputum acid-fast stains and cultures (plus PCR, if available) for pulmonary disease or tissue sampling for extrapulmonary sites. We also send tuberculin skin test (TST) and interferon-gamma release assay (IGRA) tests if we suspect tuberculosis, but studies suggest that most patients with active tuberculosis have negative results.

- **Disseminated endemic fungal infection** – Outdoor exposure in certain locales (eg, the midwestern United States, deserts of the western United States) is a risk factor for endemic mycoses. Diagnostic tests are discussed elsewhere. (See "Diagnosis and treatment of disseminated histoplasmosis in patients without HIV", section on 'Diagnostic methods' and "Clinical manifestations and diagnosis of blastomycosis" and "Coccidioidomycosis: Laboratory diagnosis and screening" and "Mycology and epidemiology of paracoccidioidomycosis".)

- **Vasculitis** – Many laboratory studies can confirm vasculitis as can biopsy of affected tissues. (See "Overview of and approach to the vasculitides in adults".)

The scope of the potential etiologies of FUO is too broad to address in this topic. Clinicians should refer to specific UpToDate topics to determine the best tests for suspected diagnoses.

Evaluating each test result individually may lead to missed diagnoses and excessive testing. In a prospective study, diagnostic clues derived from patient evaluations led to a diagnosis in 101 of 167 patients (62 percent) [4]. However, studies suggest that an average of 15 diagnostic clues are identified per patient, and 48 to 81 percent of those clues are misleading [4,9,11].

Role of biopsy — In patients with classic FUO, tissue biopsy is often necessary to definitively diagnosis the underlying etiology.

We suggest performing a biopsy when the clinical data support a diagnosis that can be confirmed from a tissue sample, especially when the risks from biopsy are low (eg, skin biopsy).

Commonly biopsied sites in patients with FUO include the following:

- **Temporal artery** – Giant-cell arteritis is confirmed by biopsy of the temporal artery. The biopsy procedure should **not** delay the initiation of corticosteroid therapy, as discussed above. (See 'Limited role of empiric antibiotics and glucocorticoids' above.)

- **Lymph node or other unexplained masses** – Biopsies of lymph nodes and other masses are often performed for suspected malignancy (eg, lymphoma, metastatic cancer, solid-

organ tumor) but can also diagnose nonmalignant conditions (eg, tuberculosis, cat-scratch disease). (See "Clinical presentation and diagnosis of classic Hodgkin lymphoma in adults", section on 'Tissue biopsy' and "Tuberculous lymphadenitis", section on 'Histopathology'.)

- **Skin** – Skin biopsies are less invasive than biopsies at other anatomic sites and can have high diagnostic yield, particularly if vasculitis is suspected. (See "Evaluation of adults with cutaneous lesions of vasculitis", section on 'Skin biopsy to confirm vasculitis'.)

  Case reports describe the use of "blind" skin biopsies in patients with prolonged FUO to ultimately diagnose intravascular lymphoma, a rare form of lymphoma [24-26]. These patients often undergo prolonged workup, until skin biopsies of normal-appearing skin from the thighs, arms, or abdomen confirm the diagnosis. Given the rarity of this condition, blind biopsies are not helpful in the vast majority of patients. (See "Intravascular large B cell lymphoma", section on 'Diagnosis'.)

- **Liver** – Liver biopsy is useful in patients whose imaging suggests malignant or granulomatous lesions in the liver. Granulomatous lesions may be due to miliary tuberculosis, sarcoidosis, disseminated fungal infection (eg, histoplasmosis, coccidioidomycosis), Q fever, brucellosis, and other causes. (See "Evaluation of the adult patient with hepatic granuloma", section on 'Role of liver biopsy'.)

- **Bone marrow** – Bone marrow biopsy can be a particularly helpful diagnosis of hematologic malignancy and difficult-to-diagnose diseases such as invasive fungal or mycobacterial infections and brucellosis. Bone marrow biopsy has the highest yield in patients who have anemia, thrombocytopenia, and/or other significant hematologic abnormalities on bloodwork [27,28].

- **Bowel** – In patients suspected of having inflammatory bowel disease, large bowel biopsy can confirm the diagnosis. Small bowel biopsy can diagnose Whipple's disease.

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.

No etiology identified — For patients who continue to have fever despite thorough evaluation, several approaches may be considered.

Continued observation — For patients who appear well, we often continue serial observations with no further intervention. Fevers spontaneously resolve in most well-appearing patients (see 'Outcomes' below). Continued testing in such patients can cause unwarranted

anxiety and financial costs for the patient without increasing the likelihood of a definitive diagnosis.

Patients who continue to report fever, otherwise appear well, have had a through workup, and have never had a fever documented in clinic may have factitious fever. Factitious fever is a manifestation of an underlying psychiatric condition that causes patients to feign fever for secondary gain. Diagnosis and management of this condition is challenging. Further information regarding this condition is found separately. (See "Fever of unknown origin in adults: Etiologies", section on 'Factitious fever'.)

Whole-body imaging — Imaging the entire body has long been a feature of FUO evaluations. Historically, gallium and labelled leukocyte scans were commonly used. In the modern health care setting, PET/CT scans are increasingly utilized.

- **FDG PET/CT scans** – In centers where a positron emission tomography (PET)/computed tomography (CT) scan is available, we obtain PET/CT scans on patients with unexplained FUO who appear ill or who have ongoing concern for missed serious diagnoses such as malignancy.

  Positive PET/CT scans can identify potential causes of fever, localize sites for further evaluation (including biopsy), and guide further management. Negative results can help to exclude focal disease as the cause of fever and have been shown to be a good predictor of spontaneous resolution of fever [29,30].

  Overall, meta-analysis data of patients with classic FUO report a sensitivity of 84 to 86 percent, specificity of 52 to 63 percent, and diagnostic yield of at least 50 percent [29,31,32]. Data suggest that earlier diagnosis can be achieved if a PET/CT scan is performed within the first one to two weeks of the FUO workup and may reduce cost by decreasing the number of expensive and invasive tests [29].

  Fluorodeoxyglucose (FDG) PET/CT performs best for patients whose fevers are due to neoplasm or infection. The most common diagnoses in patients with false-negative results were adult-onset Still's disease, tuberculosis, and polymyalgia rheumatica.

- **Labelled leukocyte and gallium scans** – We rarely utilize these tests in patients with FUO because PET/CT have better diagnostic utility.

  Gallium and labelled leukocyte tests have pooled sensitivity of 60 and 33 percent, specificity of 63 and 83 percent, and diagnostic utility of 35 and 20 percent, respectively

[29,31]. Of note, the availability of gallium tests has decreased globally due to decreased production of gallium.

Other whole-body imaging studies, such as whole-body magnetic resonance imaging (MRI) and bone scans, are not routinely utilized in patients with FUO.

Broad-range molecular testing — New techniques for detecting microorganisms are rapidly emerging and have the potential to augment or supplant traditional culture and serologic testing. These modern tests can simultaneously detect genetic and molecular components of hundreds of different microorganisms. Specific types of tests include multiplex nucleic amplification tests, 16S rRNA sequencing, whole genome sequencing, metagenomic next-generation sequencing, and others [33].

For evaluating patients with FUO, these tests are in their infancy. A systematic review of these tests in patients with FUO identified a total of eight case reports/series from 2000 to 2020 [33]. Diagnoses were made in seven of the eight studies; example diagnoses included *Abiotrophia* endocarditis, culture-negative tuberculosis, splenic abscess due to *Mycobacterium avium* complex, and disseminated *Mycoplasma* spp.

Role of empiric treatment — In patients whose fevers continue after weeks of evaluation, the likelihood of identifying an etiology diminishes, particularly for serious underlying diseases.

Some clinicians treat these patients with empiric glucocorticoids. A therapeutic trial of glucocorticoids for an inflammatory process should not replace relevant biopsies for steroid-responsive diseases such as sarcoidosis, other granulomatous diseases, or vasculitis. Furthermore, corticosteroids should not be initiated until infectious etiologies and malignancies have been convincingly excluded; glucocorticoids may worsen infections and mask malignancies.

For these patients, we advise antipyretics if they provide symptomatic relief. We do not provide empiric antibiotics because the probability of infection is low in these patients, and all antibiotics have some level of associated risk.

Indications for consultation — Clinicians may elect to consult specialists, particularly for ill-appearing patients whose initial evaluation is unrevealing. Such specialists may include infectious diseases specialists, rheumatologists, and/or hematologist/oncologists.

OUTCOMES

Studies have estimated that up to half of patients with classic FUO remain without an etiologic diagnosis [4-9,34,35]. In a meta-analysis of 19 prospective observational studies published worldwide (Europe and Asia) from 1997 to 2021, including almost 2700 patients with FUO, 22 percent went undiagnosed [34].

Most adults who remain undiagnosed after an extensive evaluation have a good prognosis [7,8,34,36]. In the above-mentioned meta-analysis, fever resolved spontaneously in 59 percent of undiagnosed patients [34]. Favorable prognosis was also illustrated in a study of almost 200 patients in Belgium with FUO, 61 of whom (30 percent) were discharged from the hospital without a diagnosis. Of those without a diagnosis [36]:

- Thirty-one (51 percent) became symptom-free during hospitalization or shortly following discharge.
- Eighteen (30 percent) had persisting or recurring fever for several months or even years after discharge, without any other sequelae.
- Four were treated with glucocorticoids, and six required intermittent therapy with nonsteroidal anti-inflammatory drugs.
- Six died, but the cause of death was considered to be related to the disease that caused FUO in only two cases.

The overall mortality rate in the above meta-analysis was 11 percent and dependent on the underlying etiology of the FUO [34]. For malignancies, mortality was 48 percent compared to 27 percent for infections, 7 percent for noninfectious inflammatory conditions, and 5 percent for miscellaneous conditions such as pulmonary embolism.

SUMMARY AND RECOMMENDATIONS

- **Definition of classic fever of unknown origin (FUO)** – The traditional definition for classic FUO is a temperature >38.3˚C (100.9˚F) recorded on several occasions for >3 weeks without an established etiology despite intensive evaluation. Some experts have proposed that the temperature cutoff be lowered to >38.0˚C (100.4˚F). (See 'Definitions and categories of fuo' above.)

  Patients with recent health care exposure, underlying immunocompromise, or recent travel are excluded from the definition of classic FUO (table 1).

- **Pace of evaluation** – Because patients diagnosed with classic FUO have had prolonged fever, many can undergo an initial or sequential outpatient evaluations instead of being hospitalized. (See 'Initial evaluation and management' above.)

- **History and physical examination** – The importance of obtaining a detailed history and examination cannot be overstated. The gathered information will often guide the clinical evaluation (table 3). (See 'Obtaining a history' above and 'Physical examination' above.)

- **Initial diagnostic evaluation** – We send a panel of initial tests in all patients with classic FUO, and we add additional tests during the initial evaluation if the history or physical examination is suggestive of specific diagnoses (table 2).

  Our minimum initial testing panel includes (see 'Basic tests for all patients' above):

  - Complete blood count with differential and peripheral smear
  - Complete metabolic panel including calcium
  - Liver biochemical tests
  - Two sets of blood cultures obtained from two separate sites (obtain before any antibiotics and incubate the cultures for a minimum of five days)
  - Urinalysis with reflex urine culture
  - HIV antigen/antibody testing with reflex to confirmatory testing
  - Antinuclear antibodies
  - Rheumatoid factor
  - Heterophil antibody or Epstein-Barr antibody tests in young adults
  - Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
  - Ferritin
  - Thick and thin blood smears for malaria in endemic areas
  - CT scan of the chest, abdomen, and pelvis (table 3) (see 'Initial diagnostic testing' above)

- **Additional testing, including biopsy** – During the initial visit and subsequent visits, further tests should be obtained to target any suspected etiologies. A biopsy is appropriate if the clinical data support a diagnosis that can be confirmed from a tissue sample (table 2). (See 'Subsequent evaluation and management' above.)

- **Limited role of empiric antibiotics and glucocorticoids** – We do not administer empiric antibiotic therapy to patients with FUO unless they are suspected of having a potentially life-threatening infection.

For patients strongly suspected of having giant-cell arteritis, prompt empiric corticosteroid is indicated to prevent complications. For other patients with FUO, we do not administer empiric glucocorticoids unless the patient is severely ill and suspected of having a steroid-responsive illness.

- **Outcome** – Up to half of patients with classic FUO remain without an etiologic diagnosis after extensive evaluation. Most adults who remain undiagnosed after an extensive evaluation have a good prognosis.

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Topic 2736 Version 35.0

GRAPHICS

Category-based definitions of FUO

Category	Commonly used definition
Classic FUO	Temperature >38.3°C (100.9°F) recorded on several occasions for >3 weeks, despite 3 outpatient clinic evaluations, 1 week of intensive outpatient investigation, or 3 days of hospital-based evaluation.*
Health care-associated FUO	
▪ ICU patient	Temperature >38.3°C (100.9°F) recorded on several occasions in an ICU patient despite ≥3 days of investigations. Fever must not have been present or incubating on admission.
▪ Non-ICU patient	Same definition as for ICU patient, except patient is hospitalized but not critically ill.
▪ Post-operative patient	Same definition as for ICU patient, except fever is usually defined as ≥38.0°C (100.4°F).
FUO in immunocompromised patients¶	
▪ Neutropenic patients	Temperature ≥38.3°C (100.9°F) or ≥38.0°C (100.4°F) sustained over a one hour period, recorded on several occasions over at least 3 days, despite appropriate antimicrobial therapy. Neutropenia is defined as <500 neutrophils/microL or impending fall to that level within 48 hours.
▪ Patients with HIV and CD4 count <200 cells/microL	Temperature ≥38.3°C (100.9°F) recorded on several occasions for >3 weeks for outpatient or >3 days for inpatient despite appropriate evaluation.
Travel-associated FUO	Temperature >38.3°C (100.9°F) recorded on several occasions for >3 weeks, despite 3 outpatient clinic evaluations, 1 week of intensive outpatient investigation, or 3 days of hospital-based evaluation, in a patient who travelled to another country, typically within the prior 12 months.

FUO definitions vary. An overarching definition of FUO is fever in the absence of an identifiable cause despite reasonable evaluation in either the inpatient or outpatient setting; the fever must persist longer than typical or suspected self-limiting conditions, such as common viral illnesses. A specific temperature threshold to define a fever is debatable as well; most studies define fever as a temperature >38.3°C (100.9°F), although definitions range from 38.0°C (100.4°F) to 38.5°C (101.3°F).

FUO: fever of unknown origin.

* Because peak normal temperature in well individuals is 38.0°C, some experts have proposed a cut-off temperature for classic FUO of >38.0°C (100.4°F) instead of >38.3°C (100.9°F).[1]

¶ Formal definitions for FUO have not been defined for immunocompromising conditions other than neutropenia and HIV.

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Adapted from:

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Graphic 143892 Version 1.0

Differential diagnosis of classic FUO based on symptoms and physical examination

	Infections	Noninfectious inflammatory disorders	Malignancies	Miscellan
Constitutional symptoms and signs				
Triad of night sweats, weight loss, and anorexia	▪ Tuberculosis (pulmonary or extrapulmonary) ▪ Endocarditis ▪ Disseminated mycobacterial infection (miliary tuberculosis, nontuberculous mycobacteria) ▪ Disseminated fungal infection (eg, histoplasmosis, blastomycosis, coccidioidomycosis) ▪ Brucellosis ▪ Typhoid/enteric fever ▪ Q fever ▪ Visceral leishmaniasis	▪ Vasculitis (eg, ANCA-associated, giant-cell arteritis, polyarteritis nodosa)	▪ Lymphoma ▪ Renal cell carcinoma ▪ Metastatic cancer	▪ Castleman ▪ Atrial myxo ▪ Hyperthyro (fever is an uncommon ▪ Tumor necr factor recep associated syndrome (▪ Treatment bladder car intravesicle Calmette-G (BCG) ▪ Hemophag lymphohist
Head and neck				
Headache	▪ Mononucleosis (Epstein-Barr virus, acute HIV syndrome, cytomegalovirus, *Toxoplasma gondii*) ▪ Chronic meningitis (numerous causes) ▪ Typhoid/enteric fever ▪ Acute HIV syndrome	▪ Giant-cell arteritis		▪ Familial Mediterran fever ▪ Pheochrom ▪ Hemolytic-u syndrome ▪ Thrombotic thrombocyt purpura

	▪ Malaria ▪ *Bartonella quintana* infection ▪ Leptospirosis (immune phase of illness) ▪ Scrub typhus ▪ Epidemic typhus ▪ Murine typhus ▪ Q fever ▪ Schistosomiasis ▪ Rat-bite fever			
Temporal artery tenderness		▪ Giant-cell arteritis		
Transient or sustained unilateral vision loss		▪ Giant-cell arteritis (transient visual loss [amaurosis fugax])		
Abnormal fundus exam	▪ Endocarditis (Roth spots) ▪ Tuberculosis (choroid tubercle)	▪ Giant-cell arteritis (transient visual loss [amaurosis fugax])		
Red eye (eg, conjunctivitis, scleritis, uveitis)	▪ Leptospirosis (immune phase of illness) ▪ Murine typhus ▪ Endocarditis (conjunctival petechiae) ▪ Brucellosis ▪ Toxoplasma ▪ Tuberculosis	▪ Adult-onset Still's disease ▪ Vasculitis (rheumatoid, ANCA-associated, polyarteritis nodosa) ▪ Behçet syndrome ▪ Systemic lupus erythematosus		▪ Sarcoidosis ▪ Inflammatc bowel disea ▪ Medication
Sinus symptoms (eg, sinusitis)	▪ Bacterial sinusitis ▪ Dental infections	▪ ANCA-associated vasculitis		▪ Sarcoidosis

Sore throat, pharyngitis	▪ Mononucleosis (Epstein-Barr virus, *Toxoplasma gondii*) ▪ Gonococcal pharyngitis ▪ Rat-bite fever	▪ Adult-onset Still's disease ▪ Giant-cell arteritis ▪ ANCA-associated vasculitis		▪ Sarcoidosis ▪ PFAPA (peri fever with a stomatitis, pharyngitis adenitis) sy ▪ Cyclic neutr
Poor dentition; dental pain	▪ Dental infection ▪ Sinusitis	▪ Giant-cell arteritis (jaw claudication)		
Oral ulcers	▪ Acute HIV syndrome (acute HIV) ▪ Histoplasmosis ▪ Primary herpes simplex infection	▪ Systemic lupus erythematosus ▪ Behçet syndrome ▪ ANCA-associated vasculitis		▪ Crohn's dise ▪ PFAPA (peri fever with a stomatitis, pharyngitis adenitis) sy ▪ Cyclic neutr ▪ Medications
Thyroid enlargement, tenderness, or nodule				▪ Hyperthyro ▪ Subacute th
Lymph nodes				
Localized lymphadenopathy	▪ Mononucleosis (Epstein-Barr virus, acute HIV syndrome [acute HIV], cytomegalovirus, *Toxoplasma gondii*) ▪ Tuberculosis (ie, scrofula) ▪ Cat-scratch disease due to *Bartonella henselae* ▪ Tularemia (typhoidal disease)		▪ Lymphoma ▪ Head and neck cancer ▪ Breast cancer	▪ Kikuchi dise ▪ Castleman ▪ PFAPA (peri fever with a stomatitis, pharyngitis adenitis) sy

Diffuse lymphadenopathy	▪ Mononucleosis (Epstein-Barr virus, acute HIV syndrome [acute HIV], cytomegalovirus, *Toxoplasma gondii*) ▪ Miliary tuberculosis ▪ Scrub typhus ▪ Oroya fever	▪ Systemic lupus erythematosus ▪ Adult-onset Still's disease	▪ Lymphoma ▪ Metastatic disease	▪ Sarcoidosis ▪ Castleman ▪ Medication
Lungs				
Cough +/– hemoptysis	▪ Mycobacterial infection (eg, tuberculosis, *M. kansasii*) ▪ Q fever ▪ Endemic mycoses (eg, histoplasmosis, blastomycosis, coccidioidomycosis) ▪ Schistosomiasis	▪ ANCA-associated vasculitis ▪ Anti-glomerular basement membrane disease ▪ Systemic lupus erythematosus	▪ Lung cancer ▪ Metastases to lung	▪ Pulmonary
Heart				
New or changed murmur	▪ Endocarditis			▪ Atrial myxo
New heart block (first-, second-, or third-degree)	▪ Endocarditis ▪ Lyme disease			
Abdomen				
Abdominal pain	▪ Common intra-abdominal conditions (eg, cholecystitis, appendicitis, diverticulitis) ▪ Viral hepatitis ▪ Liver abscess (WBC, neurtrophilia) ▪ Cholangitis ▪ Typhoid/enteric fever	▪ Behçet syndrome ▪ Vasculitis (eg, polyarteritis nodosa)		▪ Inflammato bowel disea ▪ Splenic infa to vasculitis endocarditi ▪ Hemolytic-u syndrome ▪ Thrombotic thrombocyt purpura ▪ Adrenal insufficienc

	▪ Intra-abdominal abscess ▪ Perihepatitis (Fitz-Hugh-Curtis syndrome in women with pelvic inflammatory disease) ▪ Tuberculosis ▪ Splenic abscess ▪ Coccidioidomycosis ▪ Tularemia ▪ Epidemic typhus ▪ Schistosomiasis ▪ Peritonitis in patient with cirrhosis or on peritoneal dialysis			▪ Complicatic pregnancy ▪ Familial Mediterran fever ▪ Retroperito fibrosis ▪ Mesenteric ▪ Alcoholic he ▪ Tumor necr factor recep associated syndrome (
Diarrhea	▪ Typhoid/enteric fever (constipation is more common) ▪ *Clostridium difficile* infection ▪ Schistosomiasis			▪ Inflammato bowel disea ▪ Medication
Hepatomegaly	▪ Viral hepatitis ▪ Liver abscess (including amoebic) ▪ Extrapulmonary tuberculosis ▪ Disseminated histoplasmosis ▪ Q fever ▪ Acute toxo ▪ Typhoid/enteric fever ▪ Brucellosis ▪ Oroya fever ▪ Schistosomiasis	▪ Adult-onset Still's disease	▪ Hepatocellular carcinoma ▪ Liver metastases ▪ Hepatosplenic T-cell lymphoma	▪ Sarcoidosis ▪ Castleman ▪ Treatment bladder car intravesicle Calmette-G (BCG)

Splenomegaly	▪ Mononucleosis due to Epstein-Barr virus or toxo ▪ Malaria ▪ Endocarditis (may cause splenic abscess) ▪ Disseminated histoplasmosis ▪ Typhoid/enteric fever ▪ *Bartonella quintana* infection ▪ Babesiosis ▪ Brucellosis ▪ Q fever ▪ Schistosomiasis ▪ Visceral leishmaniasis	▪ Systemic lupus erythematosus ▪ Felty syndrome	▪ Lymphoma ▪ Leukemia	▪ Sarcoidosis ▪ Hemophag lymphohist ▪ Castleman
Genitourinary				
Hematuria and/or flank pain	▪ Urinary tract infection ▪ Genitourinary tuberculosis ▪ Endocarditis ▪ Schistosomiasis ▪ Melioidosis	▪ ANCA-related vasculitis ▪ Anti-glomerular basement membrane disease ▪ Systemic lupus erythematosus	▪ Renal cell carcinoma	▪ Hemolytic-u syndrome ▪ Thrombotic thrombocyt purpura ▪ Treatment bladder car intravesicle Calmette-G (BCG)
Pelvic pain	▪ Prostatitis in men (due to enterica gram-negative bacteria, sexually transmitted infections, tuberculosis, blastomycosis, coccidioidomycosis, melioidosis) ▪ Urinary tract infection		▪ Gynecologic, urologic, or colon cancer	▪ Treatment bladder car intravesicle Calmette-G (BCG)

	▪ Gynecologic infection in women, including pelvic inflammatory disease			
Testicular swelling or tenderness	▪ Brucellosis ▪ Genitourinary tuberculosis ▪ Blastomycosis ▪ Coccidioidomycosis ▪ Sexually transmitted infections (eg, gonorrhea) ▪ Epididymitis due to enteric bacteria	▪ Polyarteritis nodosa ▪ Behçet syndrome (genital ulcers most common)		▪ Familial Mediterran fever ▪ Treatment bladder car intravesicle Calmette-G (BCG)
Back				
Back pain	▪ Bacteremia +/– endocarditis ▪ Vertebral osteomyelitis (due to common bacterial causes, brucellosis, tuberculosis, blastomycosis)		▪ Metastatic cancer	
Muscles and joints				
Myalgias	▪ Endocarditis ▪ Acute toxo ▪ *Bartonella quintana* infection (pain in shin bones is common) ▪ Babesiosis ▪ Relapsing fever due to *Borrelia* spp ▪ Leptospirosis ▪ Scrub typhus ▪ Epidemic typhus ▪ Murine typhus ▪ Q fever	▪ Vasculitis (eg, giant-cell arteritis associated with polymyalgia rheumatica) ▪ Systemic lupus erythematosus		▪ Adrenal insufficienc ▪ Familial Mediterran fever ▪ Tumor necr factor recep associated syndrome (▪ Medication

	▪ Schistosomiasis ▪ Rat-bite fever			
Diffuse arthralgias	▪ Brucellosis ▪ Endocarditis ▪ Disseminated gonococcus ▪ Relapsing fever due to *Borrelia* spp ▪ Q fever ▪ Epidemic typhus ▪ Schistosomiasis ▪ Rat-bite fever	▪ Adult-onset Still's disease ▪ Systemic lupus erythematosus ▪ Vasculitis syndromes	▪ Multiple myeloma (pain is localized to back, neck, shoulders, pelvis, hip)	▪ Sarcoidosis ▪ Adrenal insufficienc ▪ Familial Mediterran fever ▪ Medication
Inflammatory arthritis	▪ Septic arthritis ▪ Brucellosis ▪ Parvovirus B19 infection (anemia) ▪ Disseminated gonococcus ▪ Coccidioidomycosis ▪ Chronic meningococcemia (mild leukocytosis, neturophila) ▪ Rat-bite fever	▪ Rheumatoid arthritis ▪ Adult-onset Still's disease ▪ Systemic lupus erythematosus ▪ Behçet syndrome	▪ Paraneoplastic syndrome	▪ Sarcoidosis ▪ Inflammato bowel disea ▪ Crystal-indu arthropathy gout) ▪ Familial Mediterran fever ▪ Medication
Neurologic				
Recent stroke	▪ Endocarditis	▪ Vasculitis (eg, polyarteritis nodosa)		▪ Atrial myxo
Peripheral neuropathy		▪ ANCA-associated vasculitis ▪ Polyarteritis nodosa ▪ Systemic lupus erythematosus		▪ Medication
Skin				
Maculopapular rash	▪ Acute HIV syndrome (acute HIV)	▪ Adult-onset Still's disease (evanescent		▪ Medication

	▪ Typhoid/enteric fever ▪ Mononucleosis due to Epstein-Barr infection (especially after treatment of penicillin) ▪ Scrub typhus ▪ Epidemic typhus ▪ Rat-bite fever	salmon-colored rash during fever) ▪ Systemic lupus erythematosus		
Palpable purpura		▪ Vasculitis (eg, ANCA-associated vasculitis, polyarteritis nodosa)		▪ Medication
Petechiae, splinter hemorrhages	▪ Endocarditis (also can have Osler nodes or Janeway lesions on hands)		▪ Lymphoma ▪ Leukemia	
Erythema nodosum	▪ Streptococcal infection, especially pharyngitis ▪ Tuberculosis ▪ Brucellosis ▪ Endemic mycoses (eg, histoplasmosis, blastomycosis, coccidioidomycosis) ▪ Mononucleosis	▪ Behçet syndrome	▪ Lymphoma ▪ Leukemia ▪ Solid tumors	▪ Sarcoidosis ▪ Inflammato bowel disea ▪ Sweet synd ▪ Drug reacti
Pustules	▪ Disseminated gonococcus ▪ Rickettsialpox ▪ African tick bite fever ▪ Queensland tick typhus	▪ Behçet syndrome		
Mass, nodule, or eschar	▪ Blastomycosis ▪ Coccidioidomycosis ▪ Tularemia ▪ Scrub typhus			▪ Sarcoidosis

	▪ Spotted fever rickettsial infections (other than Rocky Mountain spotted fever) ▪ Melioidosis			

Graphic 143470 Version 1.0

Initial evaluation of adults with classic FUO

History of present illness
Fever history and pattern, including duration
Associated symptoms (review of systems)
Past medical history, including past infections and surgeries
Medications, including prescription, over-the-counter, cannabis, herbal supplements, and others
Family history
Social history
Close contacts and their illnesses
Travel and residential history, including regions where patient has lived since childhood or exposures to prisons or congregate living facilities
Occupational history, hobbies, and sports
Outdoor exposures, including contaminated water and injuries
Animal exposures, including pets, livestock, and wild animals
Insect exposures, including mosquitoes, ticks, lice, fleas, and mites
Food and drink habits, including exposure to contaminated water/food or unpasteurized dairy products
Smoking and illicit drug use history, including injecting, smoking, inhaling, snorting, and skin popping
Sexual history, including recent and remote sexual activity, number of sexual contacts, gender, and type of sexual activity
Recent health care exposure, including dental and outpatient care and medical care in other countries
Physical examination
Temporal arteries
Ophthalmologic examination (conjunctivae, fundoscopy)
Oral cavity (palate, teeth, gums)
Thyroid
Lymph nodes (neck, supraclavicular, axillae, groin)
Lungs
Heart
Abdomen, including liver and spleen size and rectal and prostate exam
Genitalia, including testes and epididymis in men, and gynecologic pelvic exam in women

Neurologic examination, including cranial nerves and cognition
Joints and spine
Skin and nails, including wounds under dressings and casts
Laboratory tests (if not already performed)
Complete blood count (CBC) with differential and peripheral smear
Complete metabolic panel, including calcium
Liver biochemical tests (eg, aminotransferases, alkaline phosphatase, bilirubin)
Blood cultures (two sets) obtained from two separate venous sites prior to administration of antibiotics (ask microbiology laboratory to incubate cultures for at least five days.)
Urinalysis with reflex to urine culture
HIV antigen/antibody testing with reflex confirmatory testing (add viral load if acute HIV syndrome is suspected)
Antinuclear antibodies
Rheumatoid factor
Heterophile antibody test (eg, Monospot test) or Epstein-Barr virus (EBV) antibody tests in young adults
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
Ferritin
Thick and thin blood smears for malaria, in areas where malaria is endemic
Imaging tests
CT of the chest, abdomen, and pelvis with contrast
Transthoracic echocardiogram, in patients with risk factors or signs suggestive of endocarditis

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