



likely to be associated with a serious infection. HIV should be considered as a possible cause of FUO in older patients, although it is not usually suspected early in the course of FUO.

Fever in returned travelers is most often caused by common infections, such as malaria and respiratory or urinary tract infections. However, fever caused by dengue, typhoid fever, or amebic liver abscess is increasingly identified, especially among international travelers returning from the tropics. Katayama fever is a febrile syndrome occurring after exposure to fresh water schistosomes in endemic areas. It may resolve spontaneously or may require treatment with antiparasitic agents to prevent sequelae that carry severe morbidity. A travel history should be obtained, and it may redirect the entire work-up.

Health Care–Associated Fever of Unknown Origin

Some FUOs are associated with health care practices, including surgical procedures, urinary and respiratory tract instrumentation, intravascular devices, drug therapy, and immobilization. Quality control measures are set up to minimize and avoid bloodstream infections and decubitus ulcers. Drug-related fever, septic thrombophlebitis, recurrent pulmonary emboli, and *Clostridium difficile* colitis must be considered in the work-up of hospitalized patients who develop fever greater than 38° C (100.4° F) for more than 3 days if it was not present on admission.

Immune Deficiency–Associated Fever of Unknown Origin

Immunosuppressed individuals have the highest incidence of FUO of any group of patients. Due to impaired immune responses, signs of inflammation other than fever are notoriously absent or diminished, producing atypical clinical manifestations and an absence of radiologic abnormalities for what otherwise would be readily diagnosed infections. In patients with impaired cell-mediated immunity, FUO often results from conditions other than pyogenic bacterial infections (e.g., fungi, CMV).

Neutropenia is a dangerous condition that can be considered a subclass of immunodeficiency. Persons with profound neutropenia are at high risk for bacterial and fungal infections. Episodes of fever are common in patients with neutropenia. Many episodes are short lived because they respond quickly to treatment or are manifestations of rapidly fatal infections.

Bacteremia and sepsis can cause rapid deterioration in neutropenic patients, and empirical, broad-spectrum antibiotics should be administered promptly without waiting for the results of cultures. However, only about 35% of prolonged episodes of febrile neutropenia respond to broad-spectrum antibiotic therapy. If fevers persist after 3 days of treatment with broad-spectrum antibiotics, diagnostic tests to explore fungal causes should be considered along with empirical antifungal treatment.

Human Immunodeficiency Virus–Related Fever of Unknown Origin

The primary phase of HIV infection is characterized by a mononucleosis-like illness in which fever is a prominent feature (see [Chapter 101](#)). After symptoms of the primary phase of HIV infection resolve, patients enter a long period of subclinical infection during which they are usually afebrile. In the later phases of

untreated HIV infection, episodes of fever become common, often signifying a superimposed illness. Many of these are potentially devastating opportunistic infections, which tend to manifest in atypical fashion because of the severe immunodeficiency. Patients with acquired immunodeficiency syndrome (AIDS) often have multiple infections simultaneously. After highly active antiretroviral therapy (HAART) has been started and the HIV viral load is effectively suppressed, the frequency of FUO in HIV-infected patients falls markedly.

Approach to the Patient with Fever of Unknown Origin

Evaluation of a patient with FUO typically includes verification that the patient has fever, consideration of the fever pattern, a comprehensive history, repeated physical examinations, appropriate laboratory investigations, key imaging studies, and invasive diagnostic procedures. The physical examination should scrutinize the patient more closely than usual because key physical abnormalities in patients with FUO are subtle and require repeated examinations to be appreciated.

Work-up of a patient with an FUO should focus on the history, physical examination, and initial laboratory data. In place of rational diagnostic thinking, there is a temptation to order multiple comprehensive laboratory and imaging studies. Rather than leading to a diagnosis, this shotgun approach may result in enormous expense, false-positive results, and unnecessary additional investigations that may obfuscate the true diagnosis.

A fundamental principle in the management of classic FUO is that therapy should be withheld, whenever possible, until the cause of the fever has been determined, so that treatment can be tailored to a specific diagnosis. The exception is in the setting of the immunocompromised host because rapid empirical treatment is most often needed.

SPECIFIC CONDITIONS AND EXPOSURES CAUSING FEVER

Fever after Animal Exposures

Q Fever

Q fever is a widespread zoonotic infection caused by the pathogen *Coxiella burnetii* that has acute and chronic manifestations. The primary source of infection is infected cattle, sheep, and goats. The organism can exist for months in soil and can become airborne. The onset of disease is typically abrupt, and high-grade fever (40° C or 104° F), fatigue, headache, and myalgias are the most common symptoms. Acute Q fever is usually a mild disease that resolves spontaneously within 2 weeks. Q fever endocarditis usually occurs in patients with previous valvular damage or immunocompromise, and it is often the predominant manifestation of chronic infection.

An immunofluorescence assay is the reference method for the serodiagnosis of Q fever. Consideration of doxycycline therapy is warranted only for patients who are symptomatic.

Leptospirosis

Leptospirosis is a zoonotic infection with protean manifestations caused by the spirochete *Leptospira interrogans*. It is distributed worldwide, but most clinical cases occur in the tropics. The