Fever of Unknown Origin (FUO)

The syndrome is defined as the following: (1) a temperature greater than 38.3°C on several occasions, (2) more than 3 weeks' duration of illness, and (3) failure to reach a diagnosis despite one week of inpatient investigation.

FUO is currently classified into 4 distinct categories:

- **Classic FUO:** Fever for > 3 wk with no identified cause after 3 days of hospital evaluation or ≥ 3 outpatient visits
- **Health care–associated FUO:** Fever in hospitalized patients receiving acute care and with no infection present or incubating at admission if the diagnosis remains uncertain after 3 days of appropriate evaluation
- **Immune-deficient FUO:** Fever in patients with immunodeficiencies if the diagnosis remains uncertain after 3 days of appropriate evaluation, including negative cultures after 48 h
- **HIV-related FUO:** Fever for > 3 wk in outpatients with confirmed HIV infection or > 3 days in inpatients with confirmed HIV infection if the diagnosis remains uncertain after appropriate evaluation

Etiology

- Infections (25 to 50%)
- Connective tissue disorders (10 to 20%)
- Neoplasms (5 to 35%)
- Miscellaneous (15 to 25%)

Infections are the most common cause of FUO. In patients with HIV infection, opportunistic infections (eg, TB; infection by atypical mycobacteria, disseminated fungi, or cytomegalovirus) should be sought.

Common connective tissue disorders include SLE, RA, giant cell arteritis, vasculitis, and juvenile RA of adults (adult Still disease).

The **most common neoplastic causes** are lymphoma, leukemia, renal cell carcinoma, hepatocellular carcinoma, and metastatic carcinomas. However, the incidence of neoplastic causes of FUO has been decreasing, probably because they are being detected by ultrasonography and CT, which are now widely used during initial evaluation.

Important miscellaneous causes include drug reactions, deep venous thrombosis, recurrent pulmonary emboli, sarcoidosis, inflammatory bowel disease, and factitious fever.

No cause of FUO is identified in about 10% of adults.

Evaluation

History

History aims to uncover focal symptoms and facts that suggest a cause.

History of present illness should cover duration and pattern (eg, intermittent, constant) of fever. Focal pain often indicates the location (although not the cause) of the underlying disorder. Clinicians should ask generally, then specifically, about discomfort in each body part.

Review of systems should include nonspecific symptoms, such as weight loss, anorexia, fatigue, night sweats, and headaches. Also, symptoms of connective tissue disorders (eg, myalgias, arthralgias, rashes) and GI disorders (eg, diarrhea, steatorrhea, abdominal discomfort) should be sought.

Past medical history should include disorders known to cause fever, such as cancer, TB, connective tissue disorders, alcoholic cirrhosis, inflammatory bowel disease, rheumatic fever, and hyperthyroidism. Clinicians should note disorders or factors that predispose to infection, such as immunocompromise (eg, due to disorders such as HIV infection, cancer, diabetes, or use of immunosuppressants), structural heart disorders, urinary tract abnormalities, operations, and insertion of devices (eg, IV lines, pacemakers, joint prostheses).

Drug history should include questions about specific drugs known to cause fever.

Physical examination

The skin is thoroughly inspected for focal erythema (suggesting a site of infection) and rash (eg, malar rash of SLE). Clinicians should also check for cutaneous findings of endocarditis, including painful erythematous subcutaneous nodules on the tips of digits (Osler nodes), nontender hemorrhagic macules on the palms or soles (Janeway lesions), petechiae, and splinter hemorrhages under the nails.

The entire body (particularly over the spine, bones, joints, abdomen, and thyroid) is palpated for areas of tenderness, swelling, or organomegaly; digital rectal examination and pelvic examination are included. The teeth are percussed for tenderness (suggesting apical abscess). During palpation, any regional or systemic adenopathy is noted.

The heart is auscultated for murmurs (suggesting bacterial endocarditis) and rubs (suggesting pericarditis due to a rheumatologic or infectious disorder).

Red flags

The following are of particular concern:

- Immunocompromise
- Heart murmur
- Presence of inserted devices (eg, IV lines, pacemakers, joint prostheses)
- Recent travel to endemic areas

Testing

Previous test results, particularly for cultures, are reviewed.

In addition to specific testing, the following should usually be done:

- CBC with differential
- ESR
- Liver function tests
- Serial blood cultures (ideally before antimicrobial therapy)
- HIV antibody test
- Tuberculin skin test

Urinalysis, urine culture, and chest x-ray, usually already done, are repeated only if findings indicate that they should be.

Imaging tests are guided by symptoms and signs. Typically, areas of discomfort should be imaged—eg, in patients with back pain, MRI of the spine (to check for infection or tumor); in patients with abdominal pain, CT of the abdomen. However, CT of the chest, abdomen, and pelvis should be considered to check for adenopathy and occult abscesses even when patients do not have localizing symptoms or signs.

If blood cultures are positive or heart murmurs or peripheral signs suggest endocarditis, echocardiography is done.

In general, CT is useful for delineating abnormalities localized to the abdomen or chest.

MRI is more sensitive than CT for detecting most causes of FUO involving the CNS and should be done if a CNS cause is being considered.

Venous duplex imaging may be useful for identifying cases of deep venous thrombosis.

Radionuclide scanning with indium-111–labeled granulocytes may help localize some infectious or inflammatory processes. This technique has generally fallen out of favor because it is thought to contribute very little to diagnosis, but some reports suggest that it provides a higher diagnostic yield than CT.

PET may also be useful in detecting the focus of fever.

Biopsy may be required if an abnormality is suspected in tissue that can be biopsied (eg, liver, bone marrow, skin, pleura, lymph nodes, intestine, muscle). Biopsy specimens should be evaluated by histopathologic examination and cultured for bacteria, fungi, viruses, and mycobacteria or sent for molecular (PCR) diagnostic testing. Muscle biopsy or skin biopsy of rashes may confirm vasculitis. Bilateral temporal artery biopsy may confirm giant cell arteritis in elderly patients with unexplained ESR elevation.