

Approach to Fever of Unknown Origin

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The approach to a patient presenting with fever of unknown origin (FUO) should include a comprehensive history, physical examination, and appropriate diagnostic testing

Definitions:	Common Etiologies:
<p>A. <u>Classic FUO:</u></p> <p>(1) Daily or intermittent fever > 101°F</p> <p>(2) Duration of at least 3 consecutive weeks</p> <p>(3) No source identified by clinical evaluation despite:</p> <p style="padding-left: 20px;">a.) 3 days of hospital evaluation OR</p> <p style="padding-left: 20px;">b.) 7 days of outpatient evaluation OR</p> <p style="padding-left: 20px;">c.) Three outpatient visits</p>	<p>Infection (especially TB, endocarditis, osteomyelitis, intra-abdominal abscess), malignancy (especially lymphoma, renal cell carcinoma, hepatocellular), collagen vascular disease</p>
<p>B. <u>Nosocomial FUO:</u></p> <p>(1) Daily or intermittent fever > 101°F</p> <p>(2) Hospitalized ≥ 24 hours with no fever on admission</p> <p>(3) Fever evaluation of at least 3 days</p>	<p><i>Clostridium difficile</i> colitis, drug-induced fever, alcohol/drug withdrawal, pulmonary embolism, septic thrombophlebitis, sinusitis, acalculus cholecystitis, pancreatitis</p>
<p>C. <u>Immune-deficient FUO:</u></p> <p>(1) Daily or intermittent fever > 101°F</p> <p>(2) ANC < 500/mm³</p> <p>(3) Fever evaluation of at least 3 days</p>	<p>Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus</p>
<p>D. <u>HIV-associated FUO:</u></p> <p>(1) Daily or intermittent fever > 101°F</p> <p>(2) Inpatient fever > 3 days OR</p> <p>(3) Outpatient fever > 4 weeks</p>	<p>Cytomegalovirus, <i>Mycobacterium avium-intracellulare</i> complex, <i>Pneumocystis jiroveckii</i> pneumonia, drug-induced, Kaposi's sarcoma, lymphoma</p>

History:

A comprehensive history should include questions about:

- A. The fever itself (e.g. route of measurement, peak temperature, patterns, time of day, etc.)
- B. Systemic symptoms (e.g. weight loss, decreased appetite, rash, myalgias, arthralgias, etc.)
- C. Localized symptoms (e.g. cough, urinary symptoms, headache, abdominal pain, bone pain, etc.)
- D. Travel history, sick contacts, animal contacts, family history, and sexual history
- E. Potential causes of **drug-induced fever:** diuretics, pain relievers, salicylates, anti-arrhythmic agents, anti-seizure drugs, sedatives, antihistamines, barbiturates, cephalosporins, penicillins, sulfonamides

Physical Examination:

Physical Exam Finding	Clinical Correlate
Erythema nodosum	Sarcoidosis, Tuberculosis, Histoplasmosis, IBD, Drug reaction
Heart murmur	Endocarditis, rheumatic fever
Hepatomegaly	Hepatitis, Lymphoma, Metastatic cancer, Typhoid fever
Joint swelling or pain	RA, SLE, Gout, Pseudogout, Lyme Disease, Familial Mediterranean fever, Lyme disease
Livedo reticularis	PAN, SLE, cryoglobulinemia
Lymphadenopathy: A. Generalized, tender B. Localized, non-tender	Autoimmune or infectious disease Malignancy
Relative bradycardia	Legionella, Psittacosis, Q Fever, Typhoid Fever, Babesiosis, Brucellosis, Malaria, Dengue Fever, RMSF, Lymphoma, Drug Fever
Palpable purpura	Vasculitis, Meningococemia, Rickettsial infection
Splenomegaly	EBV, CMV, hematologic malignancy, sarcoidosis, tuberculosis
Temporal artery tenderness	Temporal arteritis
Uveitis	Sarcoidosis, Tuberculosis, Toxoplasmosis, Vasculitis
Vitiligo	Autoimmune disease

Laboratory Testing:

First-Line Tests
CBC with manual differential
Chemistry panel
Liver function tests
ESR
Blood culture x 3 sets
Urinalysis and urine culture
Chest x-ray
PPD or TB QuantiFERON

If the above laboratory work-up is negative, obtain a **CT of chest, abdomen and pelvis with po/iv contrast**.

Further diagnostic testing:

A. If an **infectious** disease is suspected...

Second-Line Tests: TTE, sputum culture for AFB, HIV test, Hepatitis A, B, and C serologies, RPR, ASO titer, serology for CMV, EBV

Third-Line Tests: TEE, LP, Sinus CT, Gallium scan

B. If a **non-hematologic malignancy** is suspected...

Second-Line Tests: Mammography, Chest CT with contrast, Endoscopy, Bone Scan, Gallium Scan

Third-Line Tests: MRI of the brain, Lymph node biopsy, Skin lesion biopsy, Liver biopsy, Ex-Lap

C. If a **hematologic malignancy** is suspected...

Second-Line Tests: Peripheral smear, SPEP

Third-Line Tests: Bone marrow biopsy

D. If a **rheumatologic** disease is suspected...

Second-Line Tests: RF, ANA, cryoglobulin, ferritin

Third-Line Tests: Temporal artery biopsy, Lymph node biopsy

E. Venous Doppler studies should be obtained in relevant patients.

Keep in mind for some of these tests the **false positive rate** (which can lead to unnecessary investigations) can be similar to the rate of a helpful result. One study[‡] of 73 patients from the Netherlands seen between December 2003 and July 2005 found:

- CXR: performed in 73 patients; helpful in 6 (8%) and false-positive in 8 (11%)
- Chest CT: performed in 46 patients; helpful in 9 (20%) and false-positive in 8 (17%)
- Abdominal CT: performed in 60 patients; helpful in 12 (20%) and false-positive in 17 (28%)
- PET scan: performed in 70 patients; helpful in 23 (33%) and false-positive in 10 (14%)

[‡]Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. *Medicine (Baltimore)* 2007; 86:26.

Final Points:

- Factitious fever should be considered in patients who have some medical training or experience and a fever persisting longer than six months
- Failure to reach a definitive diagnosis of FUO occurs in up to 30% of cases
- Patients for whom no definitive diagnosis is reached generally have a favorable outcome

Adapted from Roth (2003) *Am Fam Physician* 68:2223-8