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:

**A. Classic FUO:**
1. Daily or intermittent fever > 101°F
2. Duration of at least 3 consecutive weeks
3. No source identified by clinical evaluation despite:
   a.) 3 days of hospital evaluation OR
   b.) 7 days of outpatient evaluation OR
   c.) Three outpatient visits

**Common Etiologies:**
Infection (especially TB, endocarditis, osteomyelitis, intra-abdominal abscess), malignancy (especially lymphoma, renal cell carcinoma, hepatocellular), collagen vascular disease

**B. Nosocomial FUO:**
1. Daily or intermittent fever > 101°F
2. Hospitalized ≥ 24 hours with no fever on admission
3. Fever evaluation of at least 3 days

**Common Etiologies:**
*Clostridium difficile* colitis, drug-induced fever, alcohol/drug withdrawal, pulmonary embolism, septic thrombophlebitis, sinusitis, acalculus cholecystitis, pancreatitis

**C. Immune-deficient FUO:**
1. Daily or intermittent fever > 101°F
2. ANC < 500/mm³
3. Fever evaluation of at least 3 days

**Common Etiologies:**
Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus

**D. HIV-associated FUO:**
1. Daily or intermittent fever > 101°F
2. Inpatient fever > 3 days OR
3. Outpatient fever > 4 weeks

**Common Etiologies:**

### 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:

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

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<th>First-Line Tests</th>
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<tr>
<td>CBC with manual differential</td>
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<td>Chemistry panel</td>
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<td>Liver function tests</td>
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<td>ESR</td>
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<td>Blood culture x 3 sets</td>
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<td>Urinalysis and urine culture</td>
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<tr>
<td>Chest x-ray</td>
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<td>PPD or TB QuantiFERON</td>
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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\(^\text{a}\) 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%)


**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