Fever of Unknown Origin

**Definitions:** In a 1961 paper by Petersdorf and Beeson, the authors followed the outcomes of 100 patients with the following three characteristics: 1) Fever of 38.3°C or greater on several occasions 2) Over a three week period with 3) An uncertain diagnosis after one week in the hospital. This definition has been used in several case series with outcomes covering a range of etiologies. The time period generally excludes self-limited viral infections. Also, the requirement for hospitalization has been relaxed over the past several years to allow for clinical realities and more sophisticated outpatient management. One proposal is changing the third requirement to 3 outpatient visits or 3 hospital days. In a literature review, the prevalence of fever of unknown origin in hospitalized patients was estimated to be 2.9%

Strictly speaking, patients with true FUO must have the above characteristics, as well as an unremarkable history (except for fever), normal physical exam, and the following normal lab studies: CBC with diff, serum chemistries, liver function tests, rheumatoid factor, ANA, hepatitis serologies, urinalysis, three blood cultures, PPD, and a normal chest radiograph. Some authors do not specify that lab values must be normal, however. Pediatric patients, patients with HIV/AIDS, and immunosuppressed patients are considered separately.

The five main etiologies have included infectious causes (30-50%), malignancies (20-30%), rheumatologic (10-20%), miscellaneous (15-25%), and no diagnosis (5-15%). Because of changing diagnostic techniques, the relative percentages of these causes have changed over the past forty years.

**Common Etiologies:** An exhaustive list of FUO causes would include over 200 entities. The most common causes as described by multiple case series are as follows:

**Infectious:** Miliary tuberculosis, abscesses of the abdomen or pelvis, osteomyelitis, and endocarditis.

**Malignancies:** Leukemia, non-Hodgkin’s lymphoma, renal cell carcinoma, and tumors involving the liver.

**Inflammatory:** Giant cell arteritis, polyarteritis nodosa, Wegener’s granulomatosis, mixed cryoglobulinemia.

**Miscellaneous causes:** Drug fever, erythema multiforme, granulomatous hepatitis, pulmonary embolism, and sarcoidosis.

**Recommendations for Evaluation:** Obviously, fever needs to be documented to qualify. But, fever patterns have not shown to be useful in diagnosis except for malaria and cyclical neutropenia. As is the case for all diagnostic challenges, history and physical exam are key. Physical examination must include the skin, temples, fundoscopic examination, oral cavity, lymph nodes, thyroid, genitalia, and prostate exam in men and pelvic exam in women.

Lab testing should include CBC with smear, chemistries, LFT’s, UA and culture, as well as three blood cultures over 24 to 48 hours. When blood cultures are sent, the lab should be notified to test for fastidious organisms as well as routine aerobic and anaerobic organisms. ESR, chest radiograph, and placement of a PPD should be done early in the course of evaluation.

Specialized imaging such as CT of the abdomen and chest can be useful in finding abscesses and lymphadenopathy. Gallium-67 and indium-labeled WBC scans as well as bone scans can be useful to target areas for further evaluation with imaging and/or biopsy.

Serologies such as antinuclear antibody and anti-double stranded DNA are useful in younger patients. Patients with fever and lymphadenopathy can be evaluated with CMV, EBV, and HIV titers as well as PCR for acute HIV infection if this is suspected.

Biopsies should be performed when history, physical exam, other testing indicates that it may yield a diagnosis. Liver biopsy (in the setting of elevated LFT’s), temporal artery biopsy (in older patients with elevated ESR) and bone marrow biopsy (in a patient with cytopenia or positive PPD) should be considered and performed.
In a literature review by Mourad et al., the authors examined 11 papers, each describing FUO in a series of 1000 or more patients. Based on the quality of study, the authors categorized several tests and interventions based on whether 1) evidence for use of the test exists, 2) evidence against use of the test exists, 3) there is uncertainty, and 4) common tests for which no evidence exists. These are summarized as follows.

<table>
<thead>
<tr>
<th>Recommended tests for which evidence exists</th>
<th>Test for which evidence exists against use</th>
<th>Areas of uncertainty</th>
<th>Common tests for which no evidence exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal CT</td>
<td>Routine bone marrow cultures</td>
<td>Surgical exploration of the abdomen</td>
<td>ESR</td>
</tr>
<tr>
<td>Leg Doppler imaging</td>
<td></td>
<td>Empiric therapy</td>
<td>CRP</td>
</tr>
<tr>
<td>Nuclear imaging</td>
<td></td>
<td></td>
<td>MRI imaging</td>
</tr>
<tr>
<td>Duke Criteria for SBE</td>
<td></td>
<td></td>
<td>Bone scan</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td></td>
<td></td>
<td>Echocardiography</td>
</tr>
<tr>
<td>Temporal artery biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on their literature review, the authors proposed a diagnostic algorithm for evaluation of fever of unknown origin. Regarding empiric therapy, most authors discourage use of therapeutic trials (usually with antibiotics or corticosteroids) in the absence of a diagnosis. Therapy without diagnosis will often obscure further workup efforts.

**Outcomes:** As may be predicted, the prognosis for patients with fever of unknown origin depends almost entirely on the eventual diagnosis (no big surprise here!) Reassuringly, patients with FUO which remains undiagnosed usually do well. In one study of 290 patients with FUO who were followed prospectively, 80 were discharged without diagnosis, and 77 of those patients recovered without consequence.

**Bibliography:**


UpToDate: Approach to the adult with fever of unknown origin. 2004