Fever of Unknown Origin: A Clinical Approach
Burke A. Cunha, MD,a,b Olivier Lortholary, MD, PhD,c,d Cheston B. Cunha, MD,e,f

aInfectious Disease Division, Winthrop-University Hospital, Mineola, NY; bState University of New York, School of Medicine, Stony Brook; cHôpital Necker-Enfants Malades, Service des Maladies Infectieuses et Tropicales, Centre d’ Infectiologie Necker-Pasteur, IHU Imagine, Paris, France; dUniversité Paris Descartes, Paris, France; eInfectious Disease Division, Rhode Island Hospital and The Miriam Hospital, Providence; fBrown University Alpert School of Medicine, Providence, RI.

ABSTRACT
Fever of unknown origin remain one of the most difficult diagnostic challenges in medicine. Because fever of unknown origin may be caused by over 200 malignant/neoplastic, infectious, rheumatic/inflammatory, and miscellaneous disorders, clinicians often order non-clue-based imaging and specific testing early in the fever of unknown origin work-up, which may be inefficient/misleading. Unlike most other fever-of-unknown-origin reviews, this article presents a clinical approach. Characteristic history and physical examination findings together with key nonspecific test abnormalities are the basis for a focused clue-directed fever of unknown origin work-up.

CLASSIC FEVER OF UNKNOWN ORIGIN
Prolonged fevers have been diagnostically problematic since antiquity. Among the ancients, typhoid fever and malaria were common causes of prolonged fevers.1 Few infections are associated with prolonged fevers.2 Petersdorf and Bessoon3 developed criteria for prolonged fevers, that is, fever of unknown origin, defined as fever ≥38.3°C (101°F) for >3 weeks that remains undiagnosed after a hospital work-up. Fever of unknown origin work-ups may be done as an outpatient.4 Petersdorf also classified fevers of unknown origin by category, that is, infectious, malignant/neoplastic, rheumatic/inflammatory, and miscellaneous disorders (Table 1).2,5,6 Fevers of unknown origin also may be considered in the context of host subsets, for example, organ transplants, human immunodeficiency virus, returning travelers.3

There is no standard diagnostic approach to fever of unknown origin.7-11 Fever of unknown origin requires a focused fever of unknown origin-relevant history, physical examination, and selective nonspecific laboratory tests rather than excessive overtesting.11-16

Diagnostic Approach to Classic Fever of Unknown Origin
First, verify the prolonged fever meets the fever-of-unknown-origin definition.2,16-21 The fever-of-unknown-origin work-up should be symptom (history) and sign (physical examination) driven.12,13 Second, based on history and physical clues, try to determine the appropriate category for the fever.16,21,22

Each fever of unknown origin category has clinical hallmarks, for example, usually, malignant/neoplastic disorders are associated with early anorexia and significant weight loss. With infectious fevers of unknown origin, chills are common, but weight loss less pronounced and anorexia late. Excluding vasculitis, synovitis is the rheumatic/inflammatory hallmark. While hallmark features suggest particular fever of unknown origin categories, some findings essentially eliminate a fever-of-unknown-origin category, for example, rigors eliminate the rheumatic/inflammatory category of fever.11,13,21

Third, within the fever-of-unknown-origin category, try to determine the pattern of organ involvement. Each disorder has a characteristic pattern of organ involvement that suggests/limits diagnostic possibilities. For example,
pattern of organ involvement of systemic lupus erythematosus involves multiple organs but importantly, spares the liver. Similarly, while splenomegaly is a cardinal subacute bacterial endocarditis finding, hepatomegaly essentially rules out subacute bacterial endocarditis on the basis of pattern of organ involvement alone.13,21,22

The most diagnostically difficult fevers of unknown origin have no localizing signs.

Key clues may be overlooked with a thorough but not fever of unknown origin focused history and physical examination.7-10

In the fever of unknown origin focused physical examination, special attention should be given to the eyes, skin, nodes, liver, and spleen.8-10 Testing should be selective and based on diagnostic probabilities, not possibilities, for example, routine blood cultures.11

Blood cultures are useful for bacteremic fevers of unknown origin, for example, brucellosis, typhoid/enteric fever, intravascular infections, and abscesses, but blood cultures are unnecessary and may be misleading for non-bacteremic infections, malignant/neoplastic, rheumatic/inflammatory, and miscellaneous fevers of unknown origin.11,21 Subacute bacterial endocarditis is not an uncommon infection, but now is a relatively rare cause of fever of unknown origin.14,18,22

**History**

**Malignant/Neoplastic Disorders.** Significant weight loss (>2 lbs/week), particularly if accompanied by early anorexia, is a hallmark of malignant/neoplastic fevers of unknown origin.23-25 Post-hot bath pruritus suggests a malignant/neoplastic disorder.23-26 A malignant/neoplastic fever of unknown origin should be considered in those with a history of adenopathy or malignancy.

**Infectious Diseases.** The history should include prior/invasive procedures or surgeries (abscesses), dentition (apical abscesses, subacute bacterial endocarditis), antecedent/concomitant infections, and tuberculosis.16,21 Animal or pet contact suggests Q fever, brucellosis, toxoplasmosis, cat scratch disease, or systemic lupus erythematosus.26-28 Mosquito or tick exposure suggests ehrlichiosis/anaplasmosis, babesiosis, or malaria, while rodent exposure suggests rat bite fever, relapsing fever, or leptospirosis.15,21,26 Blood transfusions may be an important clue to ehrlichiosis/anaplasmosis, babesiosis, cytomegalovirus, or human immunodeficiency virus. In normal hosts, the only clue to cytomegalovirus may be secretion exposure.27 Immunosuppressive drugs predispose to particular pathogens, for example, cytomegalovirus, tuberculosis. Disparate multiple symptoms/signs suggest multisystem disease, for example, miliary tuberculosis or Whipple’s disease, rather than several different disorders.4,21

**Rheumatic/Inflammatory Disorders.** With prominent arthralgias/myalgias, a rheumatic/inflammatory fever of unknown origin is likely, but chills argue against a rheumatic/inflammatory etiology.28,30 Dry cough may also be a subtle clue of giant cell arteritis/temporal arteritis.31 With a fever of unknown origin, oral ulcers suggest Behçet’s syndrome or systemic lupus erythematosus.28,29 The pattern of organ involvement in a fever of unknown origin with a history of joint symptoms and generalized lymphadenopathy points to adult Still’s disease or systemic lupus erythematosus.26,30 A history of acalculous cholecystitis in a fever of unknown origin is an easily overlooked clue of systemic lupus erythematosus or periarteritis nodosa.26,30 A family history is important if Behçet’s disease is being considered.

**Miscellaneous Disorders.** If the history does not suggest a particular category, miscellaneous causes of fever of unknown origin should be considered. Fever periodicity may be the only clue to cyclic neutropenia.32 A history of lymphadenopathy may suggest Rosai-Dorfman or Kikuchi’s disease.33,34 Neck/jaw pain, easily dismissed as dental pain, may be a clue to subacute thyroïditis.35-38 Factitious fever should be considered in medical personnel.39 Specifically, inquire about inflammatory bowel disease (regional enteritis), alcoholism (cirrhosis), and medications (pseudolymphoma, drug fever).26,40 Some miscellaneous fevers of unknown origin are familial, for example, familial Mediterranean fever or hyper-IgD syndrome.41,42

**Physical Examination**

**Malignant/Neoplastic Disorders.** Hectic fevers of lymphoma may resemble infection.23,25,43 Relative bradycardia may accompany lymphoma or central nervous system malignancy.26,44,45 Eye examination may be helpful, for example, Roth spots (lymphoma, atrial myxoma), cytoid bodies (atrial myxoma), or retinal hemorrhages (preleukemia).45,46 A murmur is a key finding in subacute bacterial endocarditis, noninfectious culture-negative endocarditis, for example, marantic endocarditis or atrial myxoma.26,47 Sternal tenderness points to a bone marrow
disorder (preleukemia, myeloproliferative disorders). Isolated hepatomegaly in a fever of unknown origin limits diagnostic possibilities to hepatoma, renal cell carcinoma, or liver metastases.

**Infectious Diseases.** The approach to infectious fevers of unknown origin begins with fever pattern analysis. Morning temperature spikes suggest miliary tuberculosis, typhoid/enteric fever, or Whipple’s disease. Relative bradycardia is a cardinal finding in typhoid/enteric fever, malaria, babesiosis, ehrlichiosis/anaplasmosis, leptospirosis, and Q fever. Twice daily fever spikes (double quotidian fevers) suggest malaria, miliary tuberculosis, or visceral leishmaniasis. Two fever peaks per week (camel back fever curve) may be one of the few clues to ehrlichiosis/anaplasmosis, leptospirosis, brucellosis, or rat bite fever. Fundoscopic findings may be a clue to toxoplasmosis, tuberculosis, histoplasmosis, or cat scratch fever.

**Table 1** Fever of Unknown Origin (FUO): Classic Causes

<table>
<thead>
<tr>
<th>Type of Disorder</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
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<tbody>
<tr>
<td><strong>Malignancy/neoplastic disorders</strong></td>
<td>Lymphoma*&lt;br&gt;Hypernephroma/renal cell carcinoma (RCC)</td>
<td>Preleukemia (AML)<em>&lt;br&gt;Myeloproliferative disorders (MPDs)</em></td>
<td>Atrial myxoma&lt;br&gt;Multiple myeloma&lt;br&gt;Colon carcinoma&lt;br&gt;Pancreatic carcinoma&lt;br&gt;Hepatoma&lt;br&gt;CNS metastases&lt;br&gt;Liver metastases&lt;br&gt;Systemic mastocytosis*&lt;br&gt;SBE†&lt;br&gt;Periapical dental abscess*&lt;br&gt;Chronic sinusitis/mastoiditis&lt;br&gt;Subacute vertebral osteomyelitis&lt;br&gt;Aortoenteric fistula&lt;br&gt;Vascular graft infections†&lt;br&gt;Relapsing fever*&lt;br&gt;(<em>Borreia recurrentis)†&lt;br&gt;Rat bite fever</em>,†&lt;br&gt;(Streptobacillus moniliformis or Spirillum minus)&lt;br&gt;Leptospirosis&lt;br&gt;Histoplasmosis&lt;br&gt;Coccidiomycosis&lt;br&gt;Visceral leishmaniasis&lt;br&gt;(kala-azar)&lt;br&gt;LGV&lt;br&gt;Whipple’s disease*&lt;br&gt;Multicentric Castleman’s disease (MCD)<em>&lt;br&gt;Malaria</em>&lt;br&gt;Babesiosis*&lt;br&gt;Ehrlichiosis/anaplasmosis*&lt;br&gt;Chronic prostatitis&lt;br&gt;Recurrent cholangitis*,†&lt;br&gt;(with Caroli’s disease)</td>
</tr>
<tr>
<td><strong>Infectious diseases</strong></td>
<td>Miliary TB&lt;br&gt;Brucellosis*&lt;br&gt;Q fever*</td>
<td>Intraabdominal/pelvic abscess†&lt;br&gt;Intra/perinephric abscess†&lt;br&gt;Typhoid/enteric fevers*,†&lt;br&gt;Toxoplasmosis*&lt;br&gt;Cat scratch disease (CSD)*&lt;br&gt;EBV&lt;br&gt;CMV&lt;br&gt;HIV&lt;br&gt;Extrapulmonary TB (renal TB, CNS TB)</td>
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<tr>
<td><strong>Rheumatologic/inflammatory disorders</strong></td>
<td>Adult Still’s disease (juvenile rheumatoid arthritis [JRA])<em>&lt;br&gt;Giant cell arteritis (GCA)/temporal arteritis (TA)</em></td>
<td>Periarteritis nodosa/&lt;br&gt;microscopic polyangiitis (PAN/MPA)<em>&lt;br&gt;Late-onset rheumatoid arthritis (LORA)&lt;br&gt;SLE</em></td>
<td>Takayasu’s arteritis*&lt;br&gt;Kikuchi’s disease*&lt;br&gt;Sarcoidosis (CNS)&lt;br&gt;Felt’s syndrome&lt;br&gt;Behçet’s disease*&lt;br&gt;Pseudogout&lt;br&gt;Antiphospholipid syndrome (APS)&lt;br&gt;Behçet’s disease*&lt;br&gt;FAPA syndrome*&lt;br&gt;(Marshall’s syndrome)</td>
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</table>
Spinal tenderness points to subacute vertebral osteomyelitis, typhoid/enteric fever, spinal tuberculosis, or brucellosis.  

Hepatomegaly alone suggests miliary tuberculosis, Epstein-Barr virus, cytomegalovirus, typhoid/enteric fever, brucellosis, histoplasmosis, ehrlichiosis/anaplasmosis, malaria, Q fever, subacute bacterial endocarditis, cat scratch disease, and rat bite fever.  

Epididymitis/epididymal nodule is an easily overlooked sign of Epstein-Barr virus, renal tuberculosis, or brucellosis.

**Rheumatic/Inflammatory Disorders.** Morning temperature spikes are an important clue to periarteritis nodosa while a double quotidian fever is a key finding in adult Still disease.  

In a fever of unknown origin, rash, if present, suggests sarcoidosis, systemic lupus erythematosus, or adult Still’s disease.  

Unequal pulse suggests Takayasu’s arteritis.  

Lacrimal gland enlargement is a clue to late-onset rheumatoid arthritis, sarcoidosis, or systemic lupus erythematosus.  

External eye/undi may provide many diagnostic clues in rheumatic/inflammatory fevers of unknown origin, for example, cytoid bodies (systemic lupus erythematosus, giant cell arteritis/temporal arteritis, periarteritis nodosa, adult Still’s disease), Roth spots (systemic lupus erythematosus, periarteritis nodosa), or retinal artery occlusion (Takayasu’s arteritis, giant cell arteritis/temporal arteritis, systemic lupus erythematosus).  

In a fever of unknown origin, oral ulcers suggest Behçet’s disease or systemic lupus erythematosus.  

Lymphadenopathy suggests systemic lupus erythematosus, late-onset rheumatoid arthritis, or sarcoidosis.  

In a fever of unknown origin with systemic lupus erythematosus, a murmur with negative blood cultures suggests possible Libman-Sacks endocarditis.  

Hepatomegaly without splenomegaly argues against a rheumatic/inflammatory fever of unknown origin etiology.  

Epididymitis/epididymal nodules are subtle clues to periarteritis nodosa, systemic lupus erythematosus, or sarcoidosis.

**Miscellaneous Disorders.** Miscellaneous fevers of unknown origin are more likely to be diagnosed by historical clues rather than physical findings. Relative bradycardia is a clue to drug fever or factitious fever.  

Lipemia retinalis may be the only sign of hypertriglyceridemia. Lymphadenopathy may be due to pseudolymphoma or hyper-IgD syndrome.  

Cirrhosis is an often-overlooked cause of fever of unknown origin. Splenomegaly is an important clue to regional enteritis, cirrhosis, or hyper-IgD syndrome.

**Nonspecific Laboratory Tests**  
In each fever of unknown origin category, nonspecific tests often provide useful diagnostic clues. Elevated erythrocyte sedimentation rate, serum ferritin, alkaline phosphatase, and blood cultures are useful for detecting occult infections.
phosphatase, and rheumatoid factor titers are particularly useful in fever of unknown origin diagnosis. Diagnostic specificity of nonspecific laboratory abnormalities is increased when considered together. Degree of test abnormality itself limits diagnostic possibilities, for example, an elevated erythrocyte sedimentation rate is very sensitive/not specific, but a highly elevated erythrocyte sedimentation rate (>100 mm/h) narrows diagnostic possibilities to very few entities. Similarly, 6% atypical lymphocytes (drug fever, toxoplasmosis) have a different differential than 36% atypical lymphocytes (Epstein-Barr virus, cytomegalovirus). Nonspecific findings may be exclusionary clues, for example, eosinophilia argues strongly against typhoid/enteric fever.

Complete blood count often contains easily overlooked clues, for example, leukopenia, monocytosis, lymphocytosis-relative lymphopenia, eosinophilia, basophilia, atypical/abnormal lymphocytes, thrombocytosis, and thrombocytopenia. In a fever of unknown origin, an isolated alkaline phosphatase elevation suggests lymphoma. Serum protein electrophoresis also may provide diagnostic clues, for example, elevated \( \alpha_1/\alpha_2 \) globulin elevations (lymphoma, systemic lupus erythematosus); monoclonal gammopathy (multiple myeloma, hyper-IgD syndrome, multicentric Castleman’s disease); and polyclonal gammopathy (human immunodeficiency virus, cytomegalovirus, cirrhosis, sarcoidosis, malaria). Microscopic hematuria may be the only clue to subacute bacterial endocarditis, renal tuberculosis, brucellosis, periarteritis nodosa, lymphoma, or renal cell carcinoma. A common error is to order numerous non-clue-directed specific tests early in the work-up without considering the value of hallmark clinical and characteristic nonspecific laboratory clues in narrowing the differential diagnosis. Specific diagnostic testing should be ordered later in the fever of unknown origin work-up and based on narrowed diagnostic possibilities (Table 2).

A common clinical problem is to differentiate infectious from malignant/neoplastic fevers of unknown origin. While the work-up is in progress, the Naprosyn test may be done early to differentiate infectious from malignant fever of unknown origin. During the 3-day Naprosyn test, if temperatures decrease markedly, then a malignant/neoplastic disorder is likely (positive Naprosyn test). However, if fevers remain elevated/only slightly decrease, an infectious etiology is likely (negative Naprosyn test).

### Invasive Tests

Lymph node biopsy is the most frequent invasive test. If possible, anterior cervical, axillary, or inguinal node biopsies should be avoided because biopsies of these nodes are usually unhelpful/nondiagnostic and are often reported as “non-specific inflammatory changes, cannot rule out infection/malignancy.” More likely to be diagnostic are posterior cervical, supra/infraclavicular, or epitrochlear node biopsies. Hilar, mediastinal, or retroperitoneal node biopsies have a high diagnostic yield. If bone involvement is likely, bone marrow biopsy may be diagnostic, for example, myeloproliferative disorders, preleukemias (due to acute myelogenous leukemia), Gaucher’s disease, lymphoma, Erdheim-Chester disease, miliary tuberculosis, disseminated histoplasmosis, multicentric Castleman’s disease, Whipple’s disease, or typhoid/enteric fever (Table 3). When blood cultures are negative, bone marrow biopsy or culture may be positive in subacute bacterial endocarditis or typhoid/enteric fevers. Epididymal nodule biopsy may be diagnostic of brucellosis, tuberculosis, leptospirosis, rat bite fever, relapsing fever, lymphoma, systemic lupus erythematosus, periarteritis nodosa, sarcoidosis, or familial Mediterranean fever. Ileal biopsy can be done for suspected ileocecal tuberculosis or regional enteritis. With image directed percutaneous biopsies, exploratory laparotomy is now rarely needed for fever of unknown origin diagnosis.

### Fever of Unknown Origin Subsets

Aside from the classical fevers of unknown origin, there are important subsets—for example, human immunodeficiency virus, organ transplants, and returning travelers that present especially difficult diagnostic challenges.

### Fever of Unknown Origin in Human Immunodeficiency Virus

Acute human immunodeficiency virus may present as a fever of unknown origin with a mononucleosis-like syndrome with fever, rash, and lymphadenopathy. Human immunodeficiency virus patients often present with fever of unknown origin as their initial clinical manifestation of opportunistic infection or malignancy. Highly active antiretroviral therapy has reduced human immunodeficiency virus associated fevers of unknown origin in the Western world, but has not altered its etiologic spectrum. The relative frequency of causes in human immunodeficiency virus fevers of unknown origin is
<table>
<thead>
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<th>Table 2</th>
<th>FUOs: Laboratory Clues by FUO Category</th>
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<tbody>
<tr>
<td><strong>WBC abnormalities</strong></td>
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</tbody>
</table>
| Leukocytosis | Infectious: Most infections  
Rheumatic/inflammatory: Adult Still's disease (juvenile rheumatoid arthritis [JRA])  
Miscellaneous: Drug fever |
| Leukopenia | Malignant/neoplastic: Leukemias  
Infectious: Miliary TB, typhoid/enteric fever, malaria, brucellosis, visceral leishmaniasis (kala-azar), EBV, CMV, histoplasmosis, relapsing fever, ehrlichiosis/anaplasmosis  
Rheumatic/inflammatory: RA (Feltty's syndrome), Gaucher's disease, SLE, sarcoidosis  
Miscellaneous: Cyclic neutropenia |
| Relative lymphocytosis | Malignant/neoplastic: ALL, lymphomas, carcinomas, multiple myeloma  
Infectious: Whipple's disease, miliary TB, brucellosis, histoplasmosis, EBV, CMV, visceral leishmaniasis (kala-azar), toxoplasmosis, typhoid/enteric fever  
Rheumatic/inflammatory: LORA |
| Relative lymphopenia | Malignant/neoplastic: Lymphoma, cirrhosis  
Infectious: CMV, HIV, Miliary TB, typhoid/enteric fever, Q fever, brucellosis, malaria, babesiosis, histoplasmosis, ehrlichiosis/anaplasmosis, Whipple's disease  
Rheumatic/inflammatory: Sarcoïdosis, SLE, LORA  
Miscellaneous: Cirrhosis |
| Monocytosis | Malignant/neoplastic: MPDs, lymphomas  
Infectious: Miliary TB, SBE, histoplasmosis, brucellosis, visceral leishmaniasis (kala-azar), malaria, typhoid/enteric fever, babesiosis, EBV, CMV  
Rheumatic/inflammatory: Sarcoïdosis, Gaucher's disease, LORA, SLE, PAN, GCA/TA  
Miscellaneous: Regional enteritis (Crohn's disease), ulcerative colitis |
| Atypical lymphocytes | Infectious: EBV, CMV, toxoplasmosis, brucellosis, malaria, babesiosis, ehrlichiosis/anaplasmosis  
Miscellaneous: Drug fever |
| Eosinophilia | Malignant/neoplastic: Lymphomas, MPDs  
Infectious: Trichinosis, histoplasmosis, coccidiodymycosis  
Rheumatic/inflammatory: PAN, sarcoidosis  
Miscellaneous: Hyper-IgE syndrome, drug fever, regional enteritis (Crohn's disease), ulcerative colitis |
| **RBC abnormalities** | |
| Erythrophagocytosis | Malignant/neoplastic: Lymphomas, acute leukemias, multiple myeloma, MPDs  
Infectious: HIV, EBV, CMV, malaria, babesiosis, toxoplasmosis, visceral leishmaniasis (kala-azar), histoplasmosis, typhoid/enteric fever, SBE, Q fever, Miliary TB, brucellosis  
Rheumatic/inflammatory: SLE, sarcoidosis, LORA |
| Platelet abnormalities | |
| Thrombocytopenia | Malignant/neoplastic: Leukemias, lymphomas, carcinomas, MPDs, multiple myeloma  
Infectious: EBV, CMV, ehrlichiosis/anaplasmosis, malaria, babesiosis, histoplasmosis, visceral leishmaniasis (kala-azar), HIV, miliary TB, relapsing fever, brucellosis  
Rheumatic/inflammatory: Gaucher's disease  
Miscellaneous: Drugs, cirrhosis |
| Thrombocytosis | Malignant/neoplastic: Malignancies, MPDs, lymphomas  
Infectious: Miliary TB, chronic infections (eg, osteomyelitis, abscess), SBE, Q fever  
Rheumatic/inflammatory: GCA/TA, PAN  
Miscellaneous: Drugs |
| Pancytopenia | Malignant/neoplastic: Multiple myeloma, Waldenström's macroglobulinemia  
Infectious: CMV, visceral leishmaniasis (kala-azar), typhoid/enteric fever |
| **Serum test abnormalities** | |
| Erythrocyte sedimentation rate (highly elevated) | Malignant/neoplastic: Malignancies  
Infectious: SBE, osteomyelitis, abscess, Q fever  
Rheumatic/inflammatory: GCA/TA, adult Still's disease (JRA), SLE, LORA, PAN  
Miscellaneous: Cirrhosis, drug fever |
| SPEP (polyclonal gammopathy) | Malignant/neoplastic: Atrial myxoma  
Infectious: HIV, malaria, visceral leishmaniasis (kala-azar), LGV, rat bite fever, Q fever  
Rheumatic/inflammatory: SLE, PAN, Takayasu's arteritis  
Miscellaneous: Cirrhosis |
| SPEP (monoclonal gammopathy) | Malignant/neoplastic: Multiple myeloma, Waldenström's macroglobulinemia  
Infectious: CMV, visceral leishmaniasis (kala-azar), typhoid/enteric fever |
Table 2

<table>
<thead>
<tr>
<th>Factor</th>
<th>Malignant/neoplastic: Multiple myelomas, lymphomas, multiple myeloma, Waldenström’s macroglobulinemia hepatomas, liver/CNS metastases</th>
<th>Infectious: EBV, CMV, malaria, ehrlichiosis/anaplasmosis, HIV, miliary TB</th>
<th>Rheumatic/inflammatory: LORA, adult Still’s disease (JRA), SLE, GCA/TA, Kawasaki’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>cold agglutinins</td>
<td>Malignant/neoplastic: Lymphomas, multiple myeloma, Waldenström’s macroglobulinemia</td>
<td>Malignant/neoplastic: Multiple myelomas, Waldenström’s macroglobulinemia</td>
<td>Miscellaneous: Pulmonary emboli</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>Malignant/neoplastic: Malignancies</td>
<td>Infectious: Malaria, babesiosis, ehrlichiosis/anaplasmosis, SBE, histoplasmosis, miliary TB, toxoplasmosis, trichinosis, CMV</td>
<td>Rheumatic/inflammatory: Adult Still’s disease (JRA)</td>
</tr>
<tr>
<td>Serum transaminases (SGOT/SGPT)</td>
<td>Malignant/neoplastic: Multiple myeloma, pre/acute leukemias, liver metastasis, lymphomas, carcinomas</td>
<td>Infectious: liver abscess, EBV, CMV, Q fever, ehrlichiosis/anaplasmosis, malaria, histoplasmosis, HIV, miliary TB, relapsing fever</td>
<td>Rheumatic/inflammatory: Gaucher’s disease</td>
</tr>
<tr>
<td>GGT (GGTP)</td>
<td>Malignant/neoplastic: Hepatoma, liver metastases, hypernephroma/renal cell carcinoma (RCC)</td>
<td>Infectious: EBV</td>
<td>Miscellaneous: Drug fever, cirrhosis, ulcerative colitis (UC)</td>
</tr>
<tr>
<td>Rheumatoid test abnormalities</td>
<td>Malignant/neoplastic: Malignancy</td>
<td>Infectious: SBE, miliary TB, visceral leishmaniasis (kala-azar), EBV, typhoid/enteric fever</td>
<td>Rheumatic/inflammatory: Sarcomatosis, LORA, Behçet’s disease, SLE</td>
</tr>
<tr>
<td>† Ferritin levels (highly elevated)</td>
<td>Malignant/neoplastic: Preleukemias (AML), leukemias, lymphomas, multiple myeloma, Waldenström’s macroglobulinemia hepatomas, liver/CNS metastases</td>
<td>Infectious: EBV, CMV, malaria, ehrlichiosis/anaplasmosis, HIV, miliary TB</td>
<td>Rheumatic/inflammatory: SLE, LORA, sarcoidosis</td>
</tr>
<tr>
<td>† Antinuclear antibody titers (ANA)</td>
<td>Infectious: HIV, EBV, CMV, TB, SBE, visceral leishmaniasis (kala-azar), malaria</td>
<td>Rheumatic/inflammatory: SLE, LORA, sarcoidosis</td>
<td>Miscellaneous: Cirrhosis</td>
</tr>
<tr>
<td>† Angiotensin-converting enzyme levels (ACE)</td>
<td>Malignant/neoplastic: Multiple myeloma, lymphoma</td>
<td>Infectious: Miliary TB, coccidiomycosis</td>
<td>Rheumatic/inflammatory: Gaucher’s disease</td>
</tr>
</tbody>
</table>

Influenced by highly active antiretroviral therapy, CD4 count, geographical area, and endemic infection prevalence, which may provide clues to the diagnosis. Most cases of human immunodeficiency virus fevers of unknown origin are due to infection, and common noninfectious causes are malignancies and drug fevers.70,71

Worldwide, tuberculosis is the most common adult immunodeficiency syndrome defining illness. With human immunodeficiency virus fevers of unknown origin, extrapulmonary or disseminated disease is common, which become more frequent as human immunodeficiency virus progresses.73 Disseminated *Mycobacterium avium-intracellulare* was a leading cause of human immunodeficiency virus fevers of unknown origin in the Western world. Other mycobacteria causing human immunodeficiency virus fevers of unknown origin include *M. kansasii* and *M. genavense*. In human immunodeficiency virus fevers of unknown origin, a single positive blood culture or mycobacteria recovered from a sterile body site is considered evidence of disseminated *M. avium-intracellulare*.70,73

While cryptococcosis may present as human immunodeficiency virus fever of unknown origin, concomitant meningoencephalitis is frequent and justifies cerebrospinal fluid analysis.74 *Pneumocystis jirovecii* pneumonia accounts for 5%-13% of human immunodeficiency virus fevers of unknown origin, depending on regional prevalence/variation.70 *P. jirovecii* pneumonia often presents as a fever of unknown origin before respiratory symptoms with very low CD4 counts.70 Interestingly, in France (2004–2011) among 1259 patients diagnosed with *P. jirovecii* pneumonia, 666 (53%) were subsequently diagnosed with human immunodeficiency virus, while 593 (47%) were known human immunodeficiency virus infected.70

AML = acute myelogenous leukemia; CMV = cytomegalovirus; EBV = Epstein-Barr virus; FUO = fever of unknown origin; GCA = giant cell arteritis; HIV = human immunodeficiency virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus; FUO = fever of unknown origin; GCA = giant cell arteritis; HIV = human immunodeficiency virus; LORA = late-onset rheumatoid arthritis; MPDs = myeloproliferative disorders; PAN = periarthritis nodosa; RA = rheumatoid arthritis; RBC = red blood cell; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus; SPEP = serum protein electrophoresis; TA = temporal arthritis; TB = tuberculosis; WBC = white blood cell.

### Table 3  FUO: Further Focused Testing (Nonimaging Tests)

<table>
<thead>
<tr>
<th>Blood tests (if suspected by history and physical examination)</th>
<th>FUO Infectious Disease Tests</th>
<th>FUO Neoplastic Disease Tests</th>
<th>FUO Rheumatic/Inflammatory Tests</th>
<th>Miscellaneous Other Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Q fever IgM/IgG titers</td>
<td>• Ferritin*</td>
<td>• ANA*</td>
<td>• TFTs (Thyroid function tests)</td>
<td></td>
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<tr>
<td>• Brucella IgM/IgG titers</td>
<td>• LDH*</td>
<td>• Ds DNA</td>
<td>If subacute thyroiditis suspected</td>
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<tr>
<td>• Bartonella IgM/IgG titers</td>
<td>• B12 levels</td>
<td>• ACE*</td>
<td>ATAs (Antithyroid antibody tests)</td>
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<tr>
<td>• Salmonella IgM/IgG titers</td>
<td>• ACE*</td>
<td>• Antiphospholipid antibodies</td>
<td>If subacute thyroiditis suspected</td>
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<tr>
<td>• EBV IgM/IgG titers</td>
<td>• β2 microglobulins</td>
<td>• Anti-CCP titers</td>
<td>• GGTP</td>
<td></td>
</tr>
<tr>
<td>• CMV IgM/IgG titers</td>
<td></td>
<td></td>
<td>If alcoholic cirrhosis suspected</td>
<td></td>
</tr>
<tr>
<td>• HHV-8 IgM/IgG titers</td>
<td></td>
<td></td>
<td>B12 levels</td>
<td></td>
</tr>
<tr>
<td>• Culture-positive endocarditis (SBE)</td>
<td></td>
<td></td>
<td>If alcoholic cirrhosis suspected</td>
<td></td>
</tr>
<tr>
<td>Blood Cultures</td>
<td></td>
<td></td>
<td>MEFV gene studies</td>
<td></td>
</tr>
<tr>
<td>• Culture-negative endocarditis (CNE)</td>
<td></td>
<td></td>
<td>If FMF suspected</td>
<td></td>
</tr>
<tr>
<td>TTE shows a vegetation plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>negative blood cultures plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>peripheral signs of SBE present</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Noninfectious CNE (marantic endocarditis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If infectious CNE work-up negative → proceed with marantic endocarditis work-up (malignancy, lymphoma, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious CNE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If vegetation on TTE/TEE and blood cultures are negative, and peripheral signs of SBE present → proceed with infectious CNE workup (Q fever, Brucella, Bartonella, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiologic tests (if suspected by history, physical examination, or nonspecific tests)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>• TTE</td>
<td>• CT/MRI abdomen/pelvis</td>
<td>• CT/MRI abdomen</td>
<td>• Abdominal CT scan</td>
<td></td>
</tr>
<tr>
<td>If blood cultures positive for endocarditis pathogen</td>
<td>If intra-abdominal/pelvic neoplasm suspected</td>
<td>If hepatomegaly/ splenomegaly or retroperitoneal adenopathy suspected</td>
<td>If regional enteritis (Crohn’s disease) suspected</td>
<td></td>
</tr>
<tr>
<td>• TEE</td>
<td>• Gallium/indium scan</td>
<td>• CT/MRI abdomen</td>
<td>• Gallium/indium scan</td>
<td></td>
</tr>
<tr>
<td>If PVE, atrial myoma, or CNE marantic endocarditis suspected</td>
<td>If neoplasm suspected</td>
<td>If hepatomegaly/ splenomegaly or retroperitoneal adenopathy suspected</td>
<td>If regional enteritis (Crohn’s disease) suspected</td>
<td></td>
</tr>
<tr>
<td>• CT/MRI abdomen/pelvis†</td>
<td>• PET-CT scan</td>
<td></td>
<td>• Chest CT (pulmonary embolus protocol)</td>
<td></td>
</tr>
<tr>
<td>If intra-abdominal/pelvic infection suspected</td>
<td>If occult neoplasm suspected</td>
<td></td>
<td>If pulmonary emboli suspected</td>
<td></td>
</tr>
<tr>
<td>• Gallium/indium scan</td>
<td></td>
<td></td>
<td>• CT-PET scan</td>
<td></td>
</tr>
<tr>
<td>If occult infection suspected</td>
<td></td>
<td></td>
<td>If Erdheim-Chester disease suspected (bone involvement, periarticular fibrosis or “coated aorta”)</td>
<td></td>
</tr>
<tr>
<td>• Panorex film of jaws</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>If apical root abscess suspected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PET-CT scan</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>If Q fever endocarditis, infected graft/ focal vascular infection suspected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other tests (if suspected by history, physical examination, or nonspecific tests)</td>
<td></td>
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</tr>
</tbody>
</table>

Cunha et al  Fever of Unknown Origin 1138.e8
Cytomegalovirus accounts for 5% of human immunodeficiency virus fevers of unknown origin.\(^75\) Cytomegalovirus is the most common human immunodeficiency virus associated viral opportunistic infection, typically manifesting when latent cytomegalovirus reactivates with CD4 counts <100/mm\(^3\). Serum cytomegalovirus deoxyribonucleic acid is present in 55% with CD4+ count <100/mm\(^3\). Both cytomegalovirus deoxyribonucleic acid and viremia are strong predictors of death.\(^76\)\(^,\)\(^77\) Cytomegalovirus chorioretinitis remains the most common initial manifestation in 30% of adult immunodeficiency syndrome.

Disseminated Histoplasma capsulatum var. capsulatum accounted for 7% of cases of human immunodeficiency virus fevers of unknown origin in the US, but there have been imported cases in Europe.\(^78\) Histoplasmosis should be considered in human immunodeficiency virus fevers of unknown origin in endemic areas/previously history of travel to endemic areas, however remote.\(^9\) Other endemic mycoses such as coccidioidomycosis and Penicillium marneffei may present as fevers of unknown origin in advanced human immunodeficiency virus patients who have traveled/lived in endemic arid areas of the Western US, Central/South America, Southeast Asia, South China, and India.\(^80\)\(^-\)\(^82\) Skin lesions, most commonly papules with central necrotic umbilication, in 70% of human immunodeficiency virus fevers of unknown origin are due to disseminated P. marneffei.\(^82\)

Visceral leishmaniasis accounts for <5% of human immunodeficiency virus fevers of unknown origin reported in 35 countries.\(^73\) Central nervous system or pulmonary toxoplasmosis, Aspergillus sp. or Bartonella sp. infections may present as human immunodeficiency virus fevers of unknown origin.\(^81\)\(^-\)\(^86\)

Malignancies represent about 8% of human immunodeficiency virus fevers of unknown origin. Lymphomas, especially non-Hodgkin’s lymphomas, occur in 4%-7%. A higher risk of Hodgkin’s disease occurs even in highly active antiretroviral therapy-treated human immunodeficiency virus. Fevers of unknown origin due to primary brain lymphoma or Kaposi’s sarcoma (associated or not with Castleman’s disease) are less common. Other cancers, such as bronchogenic carcinoma and hepatoma, are increasingly common in human immunodeficiency virus and may present as fever of unknown origin, even in those receiving highly active antiretroviral therapy.\(^87\) In contrast to classic fevers of unknown origin, rheumatic/inflammatory disorders are rare.

In human immunodeficiency virus fevers of unknown origin, drug fever is common (3%-20%). Drug-related rashes are estimated to be 100× more common in those infected with human immunodeficiency virus than in the general population. Isolated drug fever is responsible for 1.7%, and maculopapular/pruritic rash for 17% of all adverse drug reactions.\(^88\)\(^,\)\(^89\) Multiple drugs, including highly active antiretroviral therapy, increase risk for adverse reactions. Drugs commonly involved include antimicrobials (trimethoprim-sulfamethoxazole, beta-lactam antibiotics, sulfonamides, Sulfa containing laxatives (Colace) and diuretics (Lasix)), but highly active antiretroviral therapy drugs have become increasingly important.\(^88\)\(^-\)\(^90\)

Early in highly active antiretroviral therapy, immune reconstitution inflammatory syndrome may occur. Immune

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**Table 3 Continued**

<table>
<thead>
<tr>
<th>FUO Infectious Disease Tests</th>
<th>FUO Neoplastic Disease Tests</th>
<th>FUO Rheumatic/Inflammatory Tests</th>
<th>Miscellaneous Other Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naprosyn test</td>
<td>Naprosyn test</td>
<td>Temporal artery biopsy</td>
<td>Low-dose steroids</td>
</tr>
<tr>
<td>If FUO DDx infection vs</td>
<td>If FUO DDx infection vs</td>
<td>If GCA/TA suspected</td>
<td>If PMR suspected (prednisone 10 mg/day diagnostic for PMR)</td>
</tr>
<tr>
<td>Malignancy suspected</td>
<td>malignancy suspected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anergy panel/PPD or T-spot</td>
<td>BM biopsy</td>
<td>ASA therapy</td>
<td></td>
</tr>
<tr>
<td>If TB suspected</td>
<td>If myelophthisic anemia/</td>
<td>If adult Still’s disease (JRA)</td>
<td></td>
</tr>
<tr>
<td>BM biopsy/culture</td>
<td>abnormal WBCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If miliary TB, SBE, brucellosis, Q fever, typhoid/enteric fevers suspected</td>
<td>If β-2 microglobulins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If lymphoma suspected</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; AML = acute myelogenous leukemia; ASA = acetylsalicylic acid; BM = bone marrow; CCP = cyclic citrullinated peptide; CMV = cytomegalovirus; CT = computed tomography; DDx = differential diagnosis; EBV = Epstein-Barr virus; FFM = familial Mediterranean fever; FUO = fever of unknown origin; GCA = giant cell arteritis; GGTP = gamma glutamyl transpeptidase; HHV-6 = human herpes virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; JRA = juvenile rheumatoid arthritis; LDH = lactate dehydrogenase; LGV = lymphogranuloma venereum; LORA = late-onset rheumatoid arthritis; MEFV = Mediterrenean fever; MPDs = myeloproliferative disorders; MRI = magnetic resonance imaging; PAN = periarteritis nodosa; PET = positron emission tomography; PM = polymyalgia rheumatica; PPD = purified protein derivative; RA = rheumatoid arthritis; RBC = red blood cell; SBE = subacute bacterial endocarditis; TA = temporal arteritis; TB = tuberculosis; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram; WBC = white blood cell.
<table>
<thead>
<tr>
<th>Disease</th>
<th>History clues</th>
<th>Physical clues</th>
<th>Laboratory clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomas (HL/NHL)</td>
<td>Treatment for HL, primary immune deficiencies, post-transplant immunosuppressive, HIV, hectic/septic fevers (Pel-Ebstein in some), night sweats, weight loss, pruritus, malabsorption symptoms (NHL), bone pain (NHL)</td>
<td>Regional adenopathy (Hodgkin’s lymphoma), hepatomegaly, splenomegaly</td>
<td>Relative lymphopenia; monocytosis; eosinophilia; basophilia; thrombocytosis; thrombocytopenia (if ITP); ↑ alkaline phosphatase, SPEP (↑ x1/x2 globulins or hypogammaglobulinemia), ↑ ferritin, ↑ cryoglobulins, ↑ cold agglutinins, ↑ LAP, ↑ haptoglobin, ↑ B12 level, ↑ β2 microglobulins, ↑ α2-antitrypsin, + Coombs test, ↓ folate, ↑ uric acid, ↑ LDH</td>
</tr>
<tr>
<td>Hypernephroma (renal cell carcinoma)</td>
<td>Von Hippel-Lindau disease, adult polycystic kidney disease, excessive phenacetin use, flank pain, hematuria</td>
<td>Flank mass, left hydrocele</td>
<td>↑ ESR, SPEP (polyclonal gammopathy), TTE/TEE (vegetations with negative blood cultures)</td>
</tr>
<tr>
<td>Preleukemia (AML)</td>
<td>Night sweats, weight loss</td>
<td>Metamyelocytes, nucleated or teardrop RBCs, ↑ ESR, ↑ LDH, ↑ ferritin, ↑ uric acid</td>
<td></td>
</tr>
<tr>
<td>Atrial myxoma</td>
<td>Heart murmur, weight loss</td>
<td>Cytoid bodies (cotton wool spots), Roth’s spots, heart murmur, splinter hemorhages</td>
<td>↑ ESR, SPEP (polyclonal gammopathy), TTE/TEE (vegetations with negative blood cultures)</td>
</tr>
<tr>
<td>Infectious culture-negative endocarditis (CNE)</td>
<td>Night sweats, weight loss, arthralgias, heart murmur, recent dental or surgical (below waist) or urologic procedure, recent or unexplained LUQ pain, back pain, recent or unexplained CVA</td>
<td>Metamyelocytes, nucleated or teardrop RBCs, ↑ ESR, ↑ LDH, ↑ ferritin, ↑ uric acid</td>
<td></td>
</tr>
<tr>
<td>Miliary TB</td>
<td>Previous TB or exposure, immunosuppressive disorder or drugs, night sweats, weight loss (with intact appetite)</td>
<td>Morning temperature spikes, choroid tubercles, hepatomegaly, splenomegaly, generalized adenopathy</td>
<td>Leukopenia, lymphopenia, thrombocytopenia, ↑ LFTs, + CT/MRI or gallium/indium scans, - PPD (anergic), + AFB smear or culture of liver or bone marrow</td>
</tr>
<tr>
<td>Typhoid/enteric fever</td>
<td>Recent contaminated food or water exposure, recent foreign travel, headache or mental status changes, night sweats, weight loss</td>
<td>Recent body secretion exposure, blood transfusions</td>
<td>Leukopenia, lymphopenia, thrombocytopenia, ↑ LFTs, + CT/MRI or gallium/indium scans, ↑ IgM titers, Salmonella spp., + blood, urine, stool or BM cultures</td>
</tr>
<tr>
<td>CMV</td>
<td>Recent body secretion exposure, blood transfusions</td>
<td>Leukopenia, relative lymphopenia, atypical lymphocytes, ↑ LFTs, gallium/indium scans, ↑ IgM titers, + CMV PCR</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>Photosensitivity, alopecia, eye symptoms, seizures, headache or mental confusion, sore throat, arthralgias, chest or abdominal pain, tender fingertips, rash, testicular pain, acalculous cholecystitis</td>
<td>Palatal petechiae, adenopathy, splenomegaly</td>
<td>Leukopenia, relative lymphopenia, atypical lymphocytes, ↑ LFTs, gallium/indium scans, ↑ IgM titers, + CMV PCR</td>
</tr>
<tr>
<td>GCA/TA</td>
<td>Depression, amaurosis fugax, headache, eye pain, myalgias, jaw pain</td>
<td>Scalp nodules, temporal artery tenderness, episcleritis, optic disc pallor, cytoid bodies (cotton wool spots), cranial nerve palsies</td>
<td>Leukopenia, relative lymphopenia, monocytosis, ↑ ferritin, ↑ ANA, cryoglobulins, ↓ complement, thrombocytopenia, SPEP (polyclonal gammopathy), ↑ DsDNA, ↑ anti-SM antibodies, ↑ antiphospholipid antibodies, proteinuria</td>
</tr>
<tr>
<td>Adult Still’s disease (JRA)</td>
<td>Eye symptoms, sore throat, truncal rash (evanescent), arthralgias</td>
<td>Conjunctival suffusion, double quotidian fever, uveitis, arthritis (late), if rash, dermatoglyphia, (Köebner’s phenomenon), adenopathy, splenomegaly</td>
<td>Marked leukocytosis count, ↑ ESR, ↑ alkaline phosphatase, ↑ ferritin</td>
</tr>
</tbody>
</table>
reconstitution inflammatory syndrome occurs in 8%-45% of human immunodeficiency virus with tuberculosis, 35% with disseminated *M. avium-intracellulare*, 8%-31% with *C. neoformans*, and 18%-62% with cytomegalovirus. Most immune reconstitution inflammatory syndrome cases occur <60 days after initiating highly active antiretroviral therapy. Immune reconstitution inflammatory syndrome is often associated with more specific, infection-associated signs such as respiratory symptoms or inflammatory adenopathies with tuberculosis or raised intracranial pressure with cryptococcosis, which are clues to the diagnosis of immune reconstitution inflammatory syndrome in human immunodeficiency virus fevers of unknown origin. Unaltered in the highly active antiretroviral therapy era, the cause of human immunodeficiency virus fevers of unknown origin remains unknown in 6%-14%. 

**Fever of Unknown Origin in Solid Organ Transplants**

The diagnostic approach to solid organ transplant fevers of unknown origin is based on 4 major factors: degree/duration of immunosuppression time of posttransplant fever of unknown origin, recent/remote epidemiological exposure (health care-related or community-acquired infections), and clinical manifestations.

Immunosuppression status is not based on a single specific biomarker, for example, CD4 counts as in human immunodeficiency virus, but is related to the additive immunosuppressive effect of underlying disease requiring transplantation, magnitude/type of immunosuppressive therapy, renal failure, diabetes, associated neutropenia, and co-infection with immunosuppressive viruses (cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus). Three different posttransplantation periods are recognized to approach the differential diagnosis of solid organ transplant fevers of unknown origin, from 1-6 months and >6 months.

Clinical symptoms should direct the diagnostic approach. Subacute/chronic meningitis suggests tuberculosis, cryptococcosis, or endemic fungi while focal brain lesions suggest nocardiosis, toxoplasmosis, aspergillosis, or lymphoma. Meningoencephalitis suggests a viral cause (cytomegalovirus, varicella-zoster virus, West Nile virus). Skin lesions...
(umbilicated papules) may suggest disseminated fungal infections (Fusarium sp.). Noninfectious causes of solid organ transplant fevers of unknown origin include drug fever/trash. Post-transplant lymphoproliferative disorders and transplant rejection may present as solid organ transplant fevers of unknown origin.\textsuperscript{70,94,95}

**Fever of Unknown Origin in Returning Travelers**

Specific fever of unknown origin etiologies in returning travelers is determined by geographical areas visited/duration of stay, eating exposures (uncooked meat/fish, shellfish, unpasteurized milk products), insect exposure (mosquitos, tick bite), and time interval after return.\textsuperscript{96,97} Ingestion of unpasteurized milk suggests possible brucellosis. In fevers of unknown origin, tick or louse-borne relapsing fevers should be considered with headache, conjunctival suffusion, and liver/spleen enlargement.\textsuperscript{98-100} In returning travelers from malarious areas, malaria should be suspected, but other causes should be considered, including viral hepatitis, typhoid/enteric fever, leptospirosis, endemic mycoses, and rickettsial diseases (Rickettsia africae or R. typhi, R. conorii, Orientia tsutsugamushi, depending on geographical area), amebic liver abscess, schistosomiasis, African trypanosomiasis, endemic arboviral infections (dengue fever, chikungunya fever, yellow fever, West Nile encephalitis, Japanese encephalitis), and acute human immunodeficiency virus.\textsuperscript{101,102}

**Easily Missed Causes of Fever of Unknown Origin**

In each fever of unknown origin category, there are some diagnoses that are particularly important either because they are easily overlooked or because they are potentially life threatening.\textsuperscript{6} The four most common/important malignant/neoplastic fevers of unknown origin that should be carefully considered are lymphoma, hypernephroma, preleukemia, and atrial myxoma. Infections that merit careful diagnostic evaluation are cytomegalovirus, miliary tuberculosis, typhoid/enteric fever, and culture-negative endocarditis. In the rheumatic/inflammatory category, systemic lupus erythematosus, giant cell arteritis/temporal arteritis, adult Still’s disease, and periarthritis nodosa may be particularly elusive diagnoses. Among miscellaneous fevers of unknown origin, drug fever, factious fever, cyclic neutropenia, and subacute thyroiditis are not to be missed diagnoses.\textsuperscript{18-50} (Table 4)

**Recurrent and Undiagnosed Fevers of Unknown Origin**

Relatively few fever of unknown origin disorders may become recurrent. Recurrent fevers of unknown origin limit diagnostic possibilities and give further opportunities for a definite diagnosis. Recurrent fevers of unknown origin may be defined as at least 2 episodes of prolonged fever separated by at least 2 weeks of fever free intervals.\textsuperscript{103} Miscellaneous disorders are more likely the longer the duration of recurrent fevers of unknown origin.\textsuperscript{104-108} The diagnostic approach to recurrent fevers of unknown origin is based on clues from serial observations/testing during/between febrile episodes, as new findings become apparent, the work-up should be redirected based on new clues.\textsuperscript{107} If a recurrent fever of unknown origin remains undiagnosed for >1 year, a definitive diagnosis is unlikely.\textsuperscript{108} Some fevers of unknown origin remain undiagnosed even after a focused diagnostic work-up. The longer that a fever of unknown origin remains undiagnosed, the less likely infectious or neoplastic etiology or a definitive diagnosis.\textsuperscript{103}

**Therapy of Fever of Unknown Origin**

Fevs of unknown origin are a diagnostic challenge and not a therapeutic problem. Until a definite fever-of-unknown-origin diagnosis, antipyretic or antimicrobial therapy may mask, delay, or obscure clinical manifestations and should be avoided.\textsuperscript{109} Empiric therapy is prudent in a few difficult-to-diagnose life-threatening fevers of unknown origin, for example, central nervous system or miliary tuberculosis, or giant cell arteritis/temporal arteritis.\textsuperscript{110}

**References**


Further Reading