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# Fever of Unknown Origin: A Clinical Approach

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**ABSTRACT**

Fevers 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.

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**KEYWORDS:** Adult fevers of unknown origin; Focused diagnostic approach; Fevers of unknown origin

## 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 Beeson[3] 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.[4]

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.[3,16-21] 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,

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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 nonbacteremic 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]

**CLINICAL SIGNIFICANCE**

- Fevers of unknown origin remain a difficult diagnostic challenge because over 200 disorders are in the differential diagnosis.
- The focused fever of unknown origin diagnostic approach is based on hallmark clinical features characteristic of each disorder. Diagnostic significance of nonspecific clinical findings is enhanced when considered together.
- The fever of unknown origin diagnostic approach should be clue driven to narrow diagnostic possibilities to direct the work-up to avoid excessive non-clue-directed testing.

## 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 trichinosis.[15,21,26] Mosquito or tick exposure suggests ehrlichiosis/anaplasmosis, babesiosis, or malaria, while rodent exposure suggests rat bite fever, relapsing fever, or leptospirosis.[13,21,26] 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.[5,21]

**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 also may 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 thyroiditis.[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).[23-26] Isolated hepatomegaly in a fever of unknown origin limits diagnostic possibilities to hepatoma, renal cell carcinoma, or liver metastases.[26,45]

**Infectious Diseases.** The approach to infectious fevers of unknown origin begins with fever pattern analysis.[48-51] Morning temperature spikes suggest miliary tuberculosis, typhoid/enteric fever, or Whipple's disease.[50,52,53] Relative bradycardia is a cardinal finding in typhoid/enteric fever, malaria, babesiosis, ehrlichiosis/anaplasmosis, leptospirosis, and Q fever.[44,45] Twice daily fever spikes (double quotidian fevers) suggest malaria, miliary tuberculosis, or visceral leishmaniasis.[52,54] 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.[26,45,52] Fundoscopic findings may be a clue to toxoplasmosis, tuberculosis, histoplasmosis, or cat scratch

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

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

**Table 1** Continued

| Type of Disorder | Common | Uncommon | Rare |
|---|---|---|---|
| Miscellaneous disorders | Drug fever*<br>Cirrhosis* | Subacute thyroiditis*<br>Regional enteritis* (Crohn's disease) | Pulmonary emboli (small/multiple)<br>Pseudolymphomas*<br>Rosai-Dorfman disease*<br>Erdheim-Chester disease (ECD)*<br>Cyclic neutropenia*<br>Familial periodic fever syndromes:<br>FMF*<br>Hyper-IgD syndrome*<br>TNF receptor-1-associated periodic syndrome (TRAPS)*<br>Schnitzler's syndrome*<br>Muckle-Wells syndrome*<br>Hypothalamic dysfunction<br>Hypertriglyceridemia (type V)*<br>Factitious fever* |

AML = acute myelogenous leukemia; APS = antiphospholipid syndrome; CMV = cytomegalovirus; CNS = central nervous system; CSD = cat scratch disease; EBV = Epstein-Barr virus; ECD = Erdheim-Chester disease; FAPA = fever, aphthous ulcers, pharyngitis, adenitis; FMF = familial Mediterranean fever; GCA = giant cell arteritis; HIV = human immunodeficiency virus; LGV = lymphogranuloma venereum; LORA = late-onset rheumatoid arthritis; MCD = multicentric Castleman's disease; MPA = microscopic polyangiitis; MPDs = myeloproliferative disorders; PAN = periarteritis nodosa; RCC = renal cell carcinoma; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus; TA = temporal arteritis; TB = tuberculosis; TNF = tumor necrosis factor.

*May present as recurrent FUOs.

†If bacteremia suspected, obtain blood cultures.

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disease.[17] Spinal tenderness points to subacute vertebral osteomyelitis, typhoid/enteric fever, spinal tuberculosis, or brucellosis.[21,55] Hepatomegaly alone suggests Q fever, typhoid/enteric fever, visceral leishmaniasis, brucellosis, rat bite fever, or relapsing fever.[21,45] Splenomegaly narrows diagnostic possibilities to 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.[21,45] Epididymo-orchitis/epididymal nodule is an easily overlooked sign of Epstein-Barr virus, renal tuberculosis, or brucellosis.[21,45]

**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.[45,51,54,55] In a fever of unknown origin, rash, if present, suggests sarcoidosis, systemic lupus erythematosus, or adult Still's disease.[54] Unequal pulse suggests Takayasu's arteritis.[21] Lacrimal gland enlargement is a clue to late-onset rheumatoid arthritis, sarcoidosis, or systemic lupus erythematosus.[26,45] External eye/fundi 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 call arteritis/temporal arteritis, systemic lupus erythematosus).[8-10,44-46] In a fever of unknown origin, oral ulcers suggest Behçet's disease or systemic lupus erythematosus.[5] Lymphadenopathy suggests systemic lupus erythematosus, late-onset rheumatoid arthritis, or sarcoidosis.[21,45] In a fever of unknown origin with systemic lupus erythematosus, a murmur with negative blood cultures suggests possible Libman-Sacks endocarditis.[28] 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.[29,30,45]

**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.[39,40,44] Lipemia retinalis may be the only sign of hypertriglyceridemia. Lymphadenopathy may be due to pseudolymphoma or hyper-IgD syndrome.[21,45] Cirrhosis is an often-overlooked cause of fever of unknown origin. Splenomegaly is an important clue to regional enteritis, cirrhosis, or hyper-IgD syndrome.[21,45]

## Nonspecific Laboratory Tests

In each fever of unknown origin category, nonspecific tests often provide useful diagnostic clues.[51,56-58] Elevated erythrocyte sedimentation rate, serum ferritin, alkaline

phosphatase, and rheumatoid factor titers are particularly useful in fever of unknown origin diagnosis.[51,59] 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,.[21,45,51] In a fever of unknown origin, an isolated alkaline phosphatase elevation suggests lymphoma.[21,23,26] 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).[45] Microscopic hematuria may be the only clue to subacute bacterial endocarditis, renal tuberculosis, brucellosis, periarteritis nodosa, lymphoma, or renal cell carcinoma.[23,45,51] 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**).[26]

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.[21,26] 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).[60,61]

## Imaging Studies

Imaging studies should be clue directed and should be selected on the basis of fever of unknown origin category and likely pattern of organ involvement.[62] With hepatic/splenic enlargement, abdominal computed tomography scans are helpful in detecting other abnormalities, for example, retroperitoneal adenopathy or intra-abdominal/pelvic abscesses/masses.[62] Gallium/indium scans are useful, but indium scans are relatively insensitive (false negative) with bone infections, for example, chronic osteomyelitis and malignancies. Cardiac echocardiography is important in culture negative endocarditis, and atrial myxoma. Positron emission tomography-computed tomography scans are most useful in detecting obscure infectious/neoplastic fevers of unknown origin, for example, lymphomas, Erdheim-Chester disease, Q fever endocarditis, or aortic graft infection.[63]

## Invasive Tests

Lymph node biopsy is the most frequent invasive test.[59] 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.[5,21,26] Hilar, mediastinal, or retroperitoneal node biopsies have a high diagnostic yield.[23] 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**).[64] When blood cultures are negative, bone marrow biopsy or culture may be positive in subacute bacterial endocarditis or typhoid/enteric fevers.[65] 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.[66,67]

## 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.[68-71]

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.[72] The relative frequency of causes in human immunodeficiency virus fevers of unknown origin is

**Table 2** FUOs: Laboratory Clues by FUO Category

| | |
|---|---|
| WBC abnormalities | |
| Leukocytosis | Infectious: Most infections<br>Rheumatic/inflammatory: Adult Still's disease (juvenile rheumatoid arthritis [JRA])<br>Miscellaneous: Drug fever |
| Leukopenia | Malignant/neoplastic: Leukemias<br>Infectious: Miliary TB, typhoid/enteric fever, malaria, brucellosis, visceral leishmaniasis (kala-azar), EBV, CMV, histoplasmosis, relapsing fever, ehrlichiosis/anaplasmosis<br>Rheumatic/inflammatory: RA (Felty's syndrome), Gaucher's disease, SLE, sarcoidosis<br>Miscellaneous: Cyclic neutropenia |
| Relative lymphocytosis | Malignant/neoplastic: ALL, lymphomas, carcinomas, multiple myeloma<br>Infectious: Whipple's disease, miliary TB, brucellosis, histoplasmosis, EBV, CMV, visceral leishmaniasis (kala-azar), toxoplasmosis, typhoid/enteric fever<br>Rheumatic/inflammatory: LORA |
| Relative lymphopenia | Malignant/neoplastic: Lymphoma, cirrhosis<br>Infectious: CMV, HIV, Miliary TB, typhoid/enteric fever, Q fever, brucellosis, malaria, babesiosis, histoplasmosis, ehrlichiosis/anaplasmosis, Whipple's disease<br>Rheumatic/inflammatory: Sarcoidosis, SLE, LORA<br>Miscellaneous: Cirrhosis |
| Monocytosis | Malignant/neoplastic: MPDs, lymphomas<br>Infectious: Miliary TB, SBE, histoplasmosis, brucellosis, visceral leishmaniasis (kala-azar), malaria, typhoid/enteric fever, babesiosis, EBV, CMV<br>Rheumatic/inflammatory: Sarcoidosis, Gaucher's disease, LORA, SLE, PAN, GCA/TA<br>Miscellaneous: Regional enteritis (Crohn's disease), ulcerative colitis |
| Atypical lymphocytes | Infectious: EBV, CMV, toxoplasmosis, brucellosis, malaria, babesiosis, ehrlichiosis/anaplasmosis<br>Miscellaneous: Drug fever |
| Eosinophilia | Malignant/neoplastic: Lymphomas, MPDs<br>Infectious: Trichinosis, histoplasmosis, coccidioidomycosis<br>Rheumatic/inflammatory: PAN, sarcoidosis<br>Miscellaneous: Hyper-IgE syndrome, drug fever, regional enteritis (Crohn's disease), ulcerative colitis |
| Basophilia | Malignant/neoplastic: Preleukemia (AML), acute leukemias, lymphomas, MPDs |
| RBC abnormalities | |
| Erythrophagocytosis | Malignant/neoplastic: Lymphomas, acute leukemias, multiple myeloma, MPDs<br>Infectious: HIV, EBV, CMV, malaria, babesiosis, toxoplasmosis, visceral leishmaniasis (kala-azar), histoplasmosis, typhoid/enteric fever, SBE, Q fever, Miliary TB, brucellosis<br>Rheumatic/inflammatory: SLE, sarcoidosis, LORA |
| Platelet abnormalities | |
| Thrombocytopenia | Malignant/neoplastic: Leukemias, lymphomas, carcinomas, MPDs, multiple myeloma<br>Infectious: EBV, CMV, ehrlichiosis/anaplasmosis, malaria, babesiosis, histoplasmosis, visceral leishmaniasis (kala-azar), HIV, miliary TB, relapsing fever, brucellosis<br>Rheumatic/inflammatory: Gaucher's disease<br>Miscellaneous: Drugs, cirrhosis |
| Thrombocytosis | Malignant/neoplastic: Malignancies, MPDs, lymphomas<br>Infectious: Miliary TB, chronic infections (eg, osteomyelitis, abscess), SBE, Q fever<br>Rheumatic/inflammatory: GCA/TA, PAN<br>Miscellaneous: Drugs |
| Pancytopenia | |
| Pancytopenia | Infectious: Miliary TB, brucellosis, histoplasmosis, ehrlichiosis/anaplasmosis, CMV, HIV<br>Rheumatic/inflammatory: Gaucher's disease, sarcoidosis, SLE |
| Serum test abnormalities | |
| ↑ Erythrocyte sedimentation rate *(highly elevated)* | Malignant/neoplastic: Malignancies<br>Infectious: SBE, osteomyelitis, abscess, Q fever<br>Rheumatic/inflammatory: GCA/TA, adult Still's disease (JRA), SLE, LORA, PAN<br>Miscellaneous: Cirrhosis, drug fever |
| SPEP (polyclonal gammopathy) | Malignant/neoplastic: Atrial myxoma<br>Infectious: HIV, malaria, visceral leishmaniasis (kala-azar), LGV, rat bite fever, Q fever<br>Rheumatic/inflammatory: SLE, PAN, Takayasu's arteritis<br>Miscellaneous: Cirrhosis |
| SPEP (monoclonal gammopathy) | Malignant/neoplastic: Multiple myeloma, Waldenström's macroglobulinemia<br>Infectious: CMV, visceral leishmaniasis (kala-azar), typhoid/enteric fever |

**Table 2** Continued

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

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

Adapted from Cunha CB. Infectious disease differential diagnosis. In: Cunha BA, Ed. *Antibiotic Essentials,* 14th ed. New Delhi, India: JP Medical Publishers; 2015:475-506.[45]

influenced by highly active antiretroviral therapy, $CD_4$ 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/variations.[70] *P. jirovecii* pneumonia often presents as a fever of unknown origin before respiratory symptoms with very low $CD_4$ 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]

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

| FUO Infectious Disease Tests | FUO Neoplastic Disease Tests | FUO Rheumatic/Inflammatory Tests | Miscellaneous Other Tests |
|---|---|---|---|
| **Blood tests** (if suspected by history and physical examination)<br>• Q fever IgM/IgG titers<br>• *Brucella* IgM/IgG titers<br>• *Bartonella* IgM/IgG titers<br>• *Salmonella* IgM/IgG titers<br>• EBV IgM/IgG titers<br>• CMV IgM/IgG titers<br>• HHV-8 IgM/IgG titers | • Ferritin*<br>• LDH*<br>• $B_{12}$ levels<br>• ACE*<br>• $\beta_2$ microglobulins | • ANA*<br>• Ds DNA<br>• ACE*<br>• Antiphospholipid antibodies<br>• Anti-CCP titers<br>• Ferritin* | • TFTs<br>(Thyroid function tests)<br>If subacute thyroiditis suspected<br>ATAs<br>(Antithyroid antibody tests)<br>If subacute thyroiditis suspected<br>• GGTP<br>If alcoholic cirrhosis suspected<br>• $B_{12}$ levels<br>If alcoholic cirrhosis suspected<br>• MEFV gene studies<br>If FMF suspected |
| **Culture-positive endocarditis (SBE)**<br>Blood Cultures | | | |
| **Culture-negative endocarditis (CNE)**<br>TTE shows a vegetation<br>*plus*<br>negative blood cultures<br>*plus*<br>peripheral signs of SBE present | | | |
| Noninfectious CNE (marantic endocarditis)<br>If *infectious CNE work-up negative* →<br>proceed with marantic endocarditis work-up (malignancy, lymphoma, etc.) | | | |
| Infectious CNE<br>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.) | | | |
| **Radiologic tests** (if suspected by history, physical examination, or nonspecific tests) | | | |
| • TTE<br>If blood cultures positive for endocarditis pathogen<br>• TEE<br>If PVE, atrial myoma, or CNE marantic endocarditis suspected<br>• CT/MRI abdomen/pelvis†<br>If intra-abdominal/pelvic infection suspected<br>• Gallium/indium scan<br>If occult infection suspected<br>• Panorex film of jaws<br>If apical root abscess suspected<br>• PET-CT scan<br>If Q fever endocarditis, infected graft/ focal vascular infection suspected | • CT/MRI abdomen/pelvis<br>If intra-abdominal/ pelvic neoplasm suspected<br>• Gallium/indium scan<br>If neoplasm suspected<br>• PET-CT scan<br>If occult neoplasm suspected | • CT/MRI abdomen<br>If hepatomegaly/ splenomegaly or retroperitoneal adenopathy suspected | • Abdominal CT scan<br>If regional enteritis (Crohn's disease) suspected<br>• Gallium/indium scan<br>If regional enteritis (Crohn's disease) suspected<br>• Chest CT (pulmonary embolus protocol)<br>If pulmonary emboli suspected<br>• CT-PET scan<br>If Erdheim-Chester disease suspected (bone involvement, periaortic fibrosis or "coated aorta") |
| Other tests (if suspected by history, physical examination, or nonspecific tests) | | | |

**Table 3** Continued

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

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; FMF = 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 = Mediterranean fever; MPDs = myeloproliferative disorders; MRI = magnetic resonance imaging; PAN = periarteritis nodosa; PET = positron emission tomography; PMR = polymyalgia rheumatica; PVE = prosthetic valve endocarditis; PPD = purified protein derivative; RA = rheumatoid arthritis; RBC = red blood cell; SBE = subacute bacterial endocarditis; TA = temporal arteritis; TB = tuberculosis; TEE = transesophageal echocardiogram; TFT = thyroid function test; TTE = transthoracic echocardiogram; WBC = white blood cell.

*Repeat if already done.

†Chest/head CT/MRI (if head/chest infectious etiology suspected).

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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 $CD_4$ counts $<100/mm^3$. Serum cytomegalovirus deoxynucleic acid is present in 55% with $CD_4+$ count $<100/mm^3$. Both cytomegalovirus deoxynucleic 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/previous history of travel to endemic areas, however remote.[79] 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.[83] 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%.[87] 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

**Table 4** FUO: Clinical Clue Summaries of Common Easily Missed Diagnoses (Malignant/Neoplastic Disorders)

| | | |
|---|---|---|
| Lymphomas (HL/NHL) | History clues: | 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) |
| | Physical clues: | Regional adenopathy (Hodgkin's lymphoma), hepatomegaly, splenomegaly |
| | Laboratory clues: | Relative lymphopenia; monocytosis; eosinophilia; basophilia; thrombocytosis; thrombocytopenia (if ITP); ↑ alkaline phosphatase, SPEP (↑ $\alpha_1/\alpha_2$ globulins or hypogammaglobulinemia), ↑ ferritin, + cryoglobulins, ↑ cold agglutinins, ↑ LAP, ↑ haptoglobin, ↑$B_{12}$ level, ↑$\beta_2$ microglobulins, ↑ $\alpha_1$-antitrypsin, + Coombs test, ↓ folate, ↑ uric acid, ↑LDH |
| Hypernephroma (renal cell carcinoma) | History clues: | Von Hippel-Lindau disease, adult polycystic kidney disease, excessive phenacetin use, flank pain, hematuria |
| | Physical clues: | Flank mass, left hydrocele |
| | Laboratory clues: | Gross/microscopic hematuria, ↑ alkaline phosphatase, ↑ GGT, ↑ calcium |
| Preleukemia (AML) | History clues: | Night sweats, weight loss |
| | Physical clues: | Sternal tenderness |
| | Laboratory clues: | Metamyelocytes, nucleated or teardrop RBCs, ↑ ESR, ↑ LDH, ↑ ferritin, ↑ uric acid |
| Atrial myxoma | History clues: | Heart murmur, weight loss |
| | Physical clues: | Cytoid bodies (cotton wool spots), Roth's spots, heart murmur, splinter hemorrhages |
| | Laboratory clues: | ↑ ESR, SPEP (polyclonal gammopathy), TTE/TEE (vegetations with negative blood cultures) |
| Infectious culture-negative endocarditis (CNE) | History clues: | 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 |
| | Physical clues: | Roth's spots, conjunctival hemorrhages, heart murmur, splinter hemorrhages, Osler's nodes, Janeway lesions, splenomegaly, spinal tenderness, joint pain or effusion |
| | Laboratory clues: | Leukocytosis, monocytosis, thrombocytosis, ↑ ESR, ↑ RF, + VDRL, microscopic hematuria |
| Miliary TB | History clues: | Previous TB or exposure, immunosuppressive disorder or drugs, night sweats, weight loss (with intact appetite) |
| | Physical clues: | Morning temperature spikes, choroid tubercles, hepatomegaly, splenomegaly, generalized adenopathy |
| | Laboratory clues: | Leukopenia, lymphopenia, thrombocytopenia, ↑ LFTs, + CT/MRI or gallium/indium scans, - PPD (anergic), + AFB smear or culture of liver or bone marrow |
| Typhoid/enteric fever | History clues: | Recent contaminated food or water exposure, recent foreign travel, headache or mental status changes, night sweats, weight loss |
| | Physical clues: | Morning temperature spikes, relative bradycardia, splenomegaly, hepatomegaly |
| | Laboratory clues: | Leukopenia, relative lymphopenia, eosinopenia, ↑ LFTs, + CT/MRI or gallium/indium scans, ↑IgM titers, *Salmonella sp.*, + blood, urine, stool or BM cultures |
| CMV | History clues: | Recent body secretion exposure, blood transfusions |
| | Physical clues: | Palatal petechiae, adenopathy, splenomegaly |
| | Laboratory clues: | Leukopenia, relative lymphopenia, atypical lymphocytes, ↑ LFTs, gallium/indium scans, ↑ IgM titers, + CMV PCR |
| SLE | History clues: | Photosensitivity, alopecia, eye symptoms, seizures, headache or mental confusion, sore throat, arthralgias, chest or abdominal pain, tender fingertips, rash, testicular pain, acalculous cholecystitis |
| | Physical clues: | Alopecia, oral ulcers, scleritis, iritis, uveitis, Roth's spots, cytoid bodies (cotton wool spots), heart murmur (if Libman-Sacks endocarditis), Osler's nodes, adenopathy, splenomegaly, epididymo-orchitis |
| | Laboratory clues: | Leukopenia, relative lymphopenia, monocytosis, ↑ ferritin, ↑ ANA, cryoglobulins, ↓ complement, thrombocytopenia, SPEP (polyclonal gammopathy), ↑ DsDNA, ↑ anti-SM antibodies, ↑ antiphospholipid antibodies, proteinuria |
| GCA/TA | History clues: | Depression, amaurosis fugax, headache, eye pain, myalgias, jaw pain |
| | Physical clues: | Scalp nodules, temporal artery tenderness, episcleritis, optic disc pallor, cytoid bodies (cotton wool spots), cranial nerve palsies |
| | Laboratory clues: | Monocytosis, ↑ ESR, ↑ alkaline phosphatase |
| Adult Still's disease (JRA) | History clues: | Eye symptoms, sore throat, truncal rash (evanescent), arthralgias |
| | Physical clues: | Conjunctival suffusion, double quotidian fever, uveitis, arthritis (late), if rash, dermatographia, (Köebner's phenomenon), adenopathy, splenomegaly |
| | Laboratory clues: | Marked leukocytosis count, ↑ ESR, ↑ alkaline phosphatase, ↑ ferritin |

**Table 4** Continued

| | | |
|---|---|---|
| PAN | History clues: | Hearing loss, watery eyes, acalculous cholecystitis, hypertension |
| | Physical clues: | Morning temperature spikes, watery eyes, episcleritis, cytoid bodies (cotton wool spots), optic neuritis (with "macular star"), Roth's spots, cranial nerve palsies, mononeuritis multiplex |
| | Laboratory clues: | ↑ ESR, ↑ alkaline phosphatase, SPEP (polyclonal gammopathy) |
| Drug fever | History clues: | Often atopic, usually sensitivity during prolonged exposure (not a recent/new drug). |
| | Physical clues: | Relative bradycardia, look "inappropriately well" for degree of fever, no rash |
| | Laboratory clues: | Leukocytosis, atypical lymphocytes, eosinophils (eosinophilia less common), ↑ ESR, mildly ↑ LFTs, blood cultures negative (excluding contaminants) |
| Subacute thyroiditis | History clues: | Often a history of antecedent viral infection, no history of thyroid disease, often history of multi-nodular goiter, headache, neck/jaw pain common, sore throat |
| | Physical clues: | Thyroid (isthmus) tenderness |
| | Laboratory clues: | Relative lymphocytosis, ↑ ESR |
| Factitious fever | History clues: | Personality disorder common, usually medical personnel, multiple hospitalizations for obscure fevers |
| | Physical clues: | Relative bradycardia, look "inappropriately well" for degree of fever |
| | Laboratory clues: | Normal CBC, LFTs, ESR, normal urine temperature <body temperature |
| Cyclic neutropenia | History clues: | Recurrent fevers, systemic symptoms occur at varying intervals but fevers always occur At 7 day multiples (usually every 21 or 28 days). |
| | Physical clues: | Unremarkable, completely well during fever free intervals |
| | Laboratory clues: | Leukopenia during febrile intervals, but WBC normal between attacks |

AML = acute monocytic leukemia; ANA = antinuclear antibody; BM = bone marrow; CBC = complete blood count; CMV = cytomegalovirus; CT = computed tomography; CVA = cerebrovascular accident; Ds DNA = double stranded deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; GGTP = gamma glutamyl transpeptidase; HIV = human immunodeficiency virus; HL = Hodgkin lymphoma; IgM = immunoglobulin M; ITP = idiopathic thrombocytopenic purpura; JRA = juvenile rheumatoid arthritis; LAP = leucine aminopeptidase; LDH = lactic acid dehydrogenase; LFT = liver function test; LUQ = left upper quadrant; MCD = multicentric Castleman disease; MPA = microscopic polyangiitis; MPDs = myeloproliferative disorders; MRI = magnetic resonance imaging; NHL = non-Hodgkin lymphoma; PAN = periarteritis nodosa; PCR = polymerase chain reaction; PPD = purified protein derivative; RBC = red blood cell; SLE = systemic lupus erythematosus; SPEP = serum protein electrophoresis; TA = temporal arteritis; TB = tuberculosis; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram; VDRL = Venereal Disease Research Laboratory test.

Adapted from: Cunha CB. Infectious disease differential diagnosis. In: Cunha BA, ed. *Antibiotic Essentials*. 14th ed. New Delhi, India: JP Medical Publishers; 2015:475-506.[45] Cunha BA. A focused diagnostic approach and non-specific tests in the diagnosis of FUO. In: Cunha BA, ed. *Fever of Unknown Origin*. New York: Informa Healthcare; 2007:9-16.[50] Cunha BA. Nonspecific tests in the diagnosis of fever of unknown origin. In: Cunha BA, ed. *Fever of Unknown Origin*. New York: Informa Healthcare; 2007:151-158.[51] Cunha BA. Fever of unknown origin (FUO). In: Gorbach SL, Bartlett JB, Blacklow NR, eds. *Infectious Diseases in Medicine and Surgery*. 3rd ed. Philadelphia: WB Saunders; 2004:1568–1577[5] and Cunha CB, Cunha BA. Fever of unknown origin (FUO). In: Schlossberg D. *Clinical Infectious Diseases,* 2nd ed. Cambridge, UK: Cambridge University Press; 2015:1-9.[6]

reconstitution inflammatory syndrome occurs in 8%-45% of human immunodeficiency virus with tuberculosis, 35% with disseminated *M. avium-intracellulare,* 8%-31% with *Cryptococcus neoformans*, and 18%-62% with cytomegalovirus. Most immune reconstitution inflammatory syndrome cases occur <60 days after initiating highly active antiretroviral therapy.[91] 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.[90] Unaltered in the highly active antiretroviral therapy era, the cause of human immunodeficiency virus fevers of unknown origin remains unknown in 6%-14%.[91]

## 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.[92]

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.[92-95]

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/rash. Post-transplant lymphoproliferative disorders and transplant rejection may present as solid organ transplant fevers of unknown origin.[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.[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.[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.[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.[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 periarteritis 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[48-50] (**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.[103] Miscellaneous disorders are more likely the longer the duration of recurrent fevers of unknown origin.[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.[107] If a recurrent fever of unknown origin remains undiagnosed for >1 year, a definitive diagnosis is unlikely.[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.[103]

## Therapy of Fever of Unknown Origin

Fevers 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.[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.[110]

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