

13. Fever – Unknown Origin

Fever of unknown origin (FUO) is a term that is often misused to describe febrile illness without an obvious etiology or without other symptoms. The definition in different studies is arbitrary, but basically refers to at least 2 weeks of daily documented fever that is unexplained despite repeated physical examinations and initial laboratory investigation, in an immunocompetent host. In approximately 12% of cases an etiology cannot be found.

Differential Diagnosis

- Infections (40%)
 - Infectious mononucleosis (EBV, CMV)
 - Other systemic viral syndromes (e.g., HIV)
 - UTI (e.g., *E. coli*)
 - Osteomyelitis (e.g., staphylococcus)
 - Upper and lower respiratory infections (sinusitis, mastoiditis, pneumonia)
 - Cat-scratch disease (*Bartonella henselae*)
 - Tuberculosis, nontuberculous mycobacterial infections
 - Abscess (abdominal or retroperitoneal)
 - CNS infections
 - Endocarditis (subacute)
 - Salmonellosis
 - Lyme disease (*Borrelia burgdorferi*)
 - Leptospirosis
 - Congenital syphilis
 - Others: Brucellosis, histoplasmosis, leishmaniasis, yersiniosis, Q fever (*Coxiella burnetii*), Rocky Mountain spotted fever (*Rickettsia rickettsii*)
- Autoimmune diseases (15%)
 - Rheumatoid arthritis accounts for 3/4 of FUO due to autoimmune diseases
 - Systemic lupus erythematosus
 - Rheumatic fever
 - Vasculitis (e.g., HSP)
 - Sarcoidosis
- Neoplastic diseases (7%)
 - Leukemia/lymphoma accounts for 80% of FUO due to malignancies
 - Neuroblastoma
 - Hepatoma
 - Soft tissue sarcoma
- Inflammatory bowel disease (3%)
- Drugs and nutritional supplements (drug fever)
- Factitious fever
- Munchausen by proxy
- Neurologic disorders
 - Familial dysautonomia
 - Central thermoregulatory disorder
 - Head injury
- Hyperthyroidism
- Anhidrotic ectodermal dysplasia
- Diabetes insipidus
- Kikuchi disease

Workup and Diagnosis

- History
 - Differentiate between FUO and multiple febrile illnesses that occur in short period of time
 - Daily documentation of fever, onset, duration
 - Weight loss, diet history, medications, sick contacts
 - Animal or tick exposure, travel, foreign contacts
 - Immune status, history of transfusion, surgery
 - FH of autoimmune or neoplastic diseases
- Physical exam
 - Vital signs, growth parameters
 - Skin (rash, desquamation, jaundice)
 - Ophthalmologic exam (conjunctivitis, uveitis)
 - Oral lesions
 - Cardiologic exam (new onset murmur)
 - Abdominal exam (masses, hepatosplenomegaly)
 - Testicular exam
 - Muscle tenderness, bone tenderness, arthritis
 - Lymphadenopathy
 - Neurologic exam
- Labs
 - CBC, ESR, C-reactive protein
 - Renal and hepatic function tests, albumin and globulin
 - Urinalysis, blood and urine culture
 - Viral titers, PPD, cultures for specific organisms, ASO, ANA, bone marrow
- Radiographic imaging with plain films, ultrasound, bone scan, CT scan or MRI of specific organ systems as warranted by the history and physical exam

Treatment

- Specific treatment once diagnosis is made
- Empiric treatment with antibiotics is to be considered only for critically ill patients
- Empiric steroids may be justified only if Still disease is suspected
- Anti-inflammatory agents are sometimes used for a limited period of time and subsequently the patient is observed for recurrence of the fever
- Cessation of offending drugs