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