Fever of Unknown Origin

Definitions:
Fever of unknown origin (FUO): Fever of 38.3 or greater of at least eight days duration, with no apparent diagnosis after initial outpatient or hospital evaluation that includes a careful history and physical exam and initial laboratory assessment. (This definition is useful for clinical purposes, but there is much variability in published studies of fever of unknown origin with required duration of fever ranging between 5-7 days to 3 weeks.)

Fever without a source (FWS): Children with fever lasting one week or less without adequate explanation after a careful history and physical examination.
- Different differential diagnosis than FUO
- Usually require immediate testing and evaluation
- Empiric treatment may be indicated for select groups of patients with FWS

Diagnostic Approach:
A careful history and physical is the first step in evaluating a patient with fever of unknown origin.

History:
- Fever
  - Duration, height and pattern, measurement technique
  - Appearance of the child during the febrile episode
  - Whether or not the fever responds to antipyretic drugs
    - Lack of response to NSAIDs may indicate a non-inflammatory condition as the cause of the fever
  - Associated sweating
    - Fever, sweating and heat intolerance may indicate hyperthyroidism
    - Fever, heat intolerance and absence of sweating is suggestive of ectodermal dysplasia
- Fever pattern:
  - Intermittent: high spike and rapid defervescence
    - Pyogenic infection
    - Can also occur in tuberculosis, lymphoma and juvenile rheumatoid arthritis
  - Remittent: fluctuating peaks and baseline that does not return to normal
    - Viral infections
    - Can occur with bacterial infections, especially endocarditis, sarcoid, lymphoma and atrial myxoma
  - Sustained: persist with little or no fluctuation
    - Typhoid fever, typhus and brucellosis
  - Relapsing: afebrile for one or more days in between febrile episodes
    - Malaria, rat bite fever, Borrelia infection and lymphoma
  - Recurrent: episodes of fever of more than six month’s duration
    - Metabolic defects
    - CNS dysregulation of temperature control
    - Periodic disorders such as cyclic neutropenia, hyperimmunoglobulin D syndrome and deficiencies of selected interleukin receptor sites
- Associated complaints
  - Include past or current complaints
- Exposure
  - Sick contacts
  - Animal exposures
    - Household pets, domestic animals in the community and wild animals
  - Travel history starting at birth
    - Site of travel
    - Prophylactic medications and immunizations for travel
    - Exposure to contaminated food and water while traveling
    - Exposure to other persons with recent travel
  - Tick or mosquito bites
  - Consumption of raw or undercooked meat or raw shellfish
  - Consumption of dirt (pica)
  - Exposure to medications
- Ethnic background
  - Ulster Scots: nephrogenic diabetes insipidus
  - Sephardic Jewish, Armenian, Turkish or Arab descent: familial Mediterranean fever
  - Ashkenazi Jewish descent: familial dysautonomias

Physical Exam
Careful physical exam which should be performed while the patient is febrile
Special attention to the following areas:
- General appearance and vital signs
- Skin and scalp
- Eyes
- Sinuses
- Oropharynx
- Lymph nodes
- Abdomen
- Musculoskeletal
- Genitourinary

Diagnostic Studies
Directed toward likely cause of fever based on information gained from the history and physical
Timing of labs and studies is based on severity of illness, ie, patients who are more ill should be evaluated with laboratory studies at a faster pace than those who appear well.

Initial Tests: CBC and peripheral smear, ESR, CRP, Aerobic blood cultures, UA, urine culture, CXR, tuberculin skin test, electrolytes, BUN, creatinine, hepatic enzymes, HIV serology
- CBC
  - Anemia: may be suggestive of malaria, infective endocarditis, IBD, SLE or tuberculosis
  - Thrombocytosis: Kawaskai disease
  - WBC: atypical lymphocytes may suggest a viral infection, immature forms may suggest leukemia and eosinophilia is suggestive of parasitic, fungal, neoplastic, allergic or immunodeficiency disorders
- ESR and CRP: non-specific acute phase reactants and general indicators of inflammation
- Blood cultures: obtain several sets if infective endocarditis is a consideration
- Urinalysis and urine culture: UTI is a common source of FUO, sterile pyuria is suggestive of Kawasaki disease or genitourinary tuberculosis
- Chest X Ray: evaluate for infiltrates or lymphadenopathy
- PPD
- Serum electrolytes, BUN, creatinine and hepatic enzymes
- HIV: significant variability in manifestations of primary HIV infection

Additional Tests: Guided by information obtained with history, physical exam and results of initial testing
- Stool studies: culture, ova and parasites in patients with loose stools or recent travel
- Bone marrow: most useful in diagnosing malignancy, histiocytic disorders and hemophagocytic disease, not helpful in diagnosing infection
- Serologies: targeted approach is indicated
  - HIV serology for all children with FUO
  - Syphilis is recommended for neonates, young infants and adolescents
  - Consider evaluation for EBV, CMV, toxoplasmosis, bartonellosis, brucellosis, tularemia as well as parasitic infections such as strongyloidiasis
- Serum anti-nuclear antibody: obtain in children over age 5 with family history of rheumatologic disease
- Immunoglobulins: serum IgG, IgA and IgM in children with evidence of recurrent or persistent infections and in those with persistent fever and a negative initial evaluation
- Molecular testing: (ie PCR) may be useful in specific cases

Imaging and other evaluations
- Abdominal imaging
  - Indicated if inflammatory bowel disease is suspected
  - Consider if fever may be due to psoas abscess or cat scratch disease
- Imaging of the nasal sinuses or mastoid is recommended if sinusitis is a possible etiology for FUO
- ECG/Echocardiography should be performed if there is concern for infective endocarditis
- Ophthalmologic exam can be helpful to evaluate uveitis or leukemic infiltration
- Biopsy is recommended only when there is evidence of specific organ involvement

Empiric Treatment
Generally avoid empiric treatment with anti-inflammatory medications or antibiotics as an effort to diagnose the patient’s condition.
- Empiric antibiotics can mask or delay diagnosis of infections such as meningitis, infectious endocarditis or osteomyelitis
- Exceptions:
  - Nonsteroidal agents in children with presumed JIA
  - Antituberculosis drugs in critically ill children with possible disseminated TB
  - Patients who are clinically deteriorating and in whom bacteremia or sepsis is strongly suspected
  - Patients who are immunocompromised
Etiologies:
- Usually caused by common disorders which may have an unusual presentation
- Most common categories are infectious disease, connective tissue diseases and neoplasms (in order of frequency)
- A diagnosis is often never established; undiagnosed cases have become more common in recent years

Generalized Infections
- Brucellosis
  - Indolent infection with persistent fever and lethargy, osteoarticular complaints, hepatosplenomegaly and mild LFT elevation
  - Consider in patients exposed to animals or animal products, especially unpasteurized cheese
- Cat scratch disease
  - Bartonella henselae infection
  - Often presents with lymph node inflammation; hepatosplenic involvement is the hallmark of FUO cases
- Leptospirosis
  - Clinical manifestation includes fever, rigors, myalgias, headache, cough and GI complaints
  - Occurs after exposure to animal urine, contaminated soil or water (swimming) or infected animal tissue
- Malaria
  - Splenomegaly typically accompanies fever
  - Should be considered in patients with history of travel to endemic areas, can present months after travel
- Mycobacterial
  - Extrapulmonary tuberculosis is more common than pulmonary TB
  - Careful history of possible contacts can help make the diagnosis
  - Nontuberculosis mycobacterium can cause disseminated infection (more common in HIV infected patients)
- Salmonellosis
  - Can cause typhoidal as well as localized GI illness
  - Diagnosis can be made with blood and stool cultures
- Toxoplasmosis
  - Most often accompanied by cervical or supraclavicular lymphadenopathy
  - Consider with exposure to feline feces or consumption of game meat
- Tularemia
  - Carried by a variety of animals and insects
  - Should be considered in children with history of animal contact, exposure to dead wild carcasses or ingestion of rabbit or squirrel meat
- Viral Infections
  - CMV, EBV, hepatitis viruses, enteroviruses and arboviruses
  - Symptoms can be non-specific and variable
  - LFTs may be elevated
Localized Infections

- Bone and joint
  - Typically present with recognizable symptoms
  - Osteomyelitis may present as FUO; locations that are more common are the pelvic bones, small bones and flat bones

- Infective endocarditis
  - Usually occurs in setting of preexisting cardiac lesion
  - Diagnosis can be difficult; blood cultures are not always positive and murmur may not be present
  - Viridans streptococci, enterococci and staphylococci are most common organisms

- Intraabdominal abscesses
  - Patients may not have abdominal complaints at presentation
  - Increased suspicion with prior intraabdominal disease, abdominal surgery or vague abdominal pain
  - Pyogenic liver abscesses are more common immunocompromised children

- Upper respiratory tract infection
  - Mastoiditis, sinusitis, chronic or recurrent otitis media, chronic or recurrent pharyngitis, tonsillitis, peritonsillar abscess and non-specific URI have all been reported as causes of FUO

- Urinary tract infection
  - Among most common cause of FUO

Connective Tissue Disease

Second most common category of FUO in children

Positive ANA is suggestive of a connective tissue disorder

- Juvenile rheumatoid arthritis (juvenile idiopathic arthritis)
  - Systemic presentation: high, spiking fevers, lymphadenopathy, and an evanescent rash which may be present only when the patient is febrile

- Polyarteritis nodosa and systemic lupus erythematosis

Neoplasms

- Leukemia and lymphoma are the most common malignancies that cause FUO in children
- Neuroblastoma, hepatoma, sarcoma and atrial myxoma are less common malignancies that may present as FUO

Other Causes

- CNS dysfunction
  - Severe brain damage and resulting autonomic dysfunction can be responsible for FUO
  - Epilepsy can cause fevers

- Diabetes insipidus
  - Central and nephrogenic DI can cause FUO

- Drug fever
  - Allergic reaction
  - Medication may impair thermoregulation ie phenothiazines, anticholinergic drugs and epinephrine
  - Typically disappears within 48-72 hours of stopping medication, but can take as long as 5-7 days or even weeks to resolve
- **Factitious fever**
  - Absence of tachycardia and diaphoresis and rapid defervescence can suggest factitious fever
  - Measurement of the temperature of a urine specimen: should parallel core body temperature and can confirm or exclude a fever

- **Familial dysautonomia**
  - Autosomal recessive disorder: autonomic and peripheral sensory nerve dysfunction results in defective temperature regulation
  - Poor swallowing coordination, excessive salivation, diminished tearing, excessive or diminished sweating, labile blood pressure, erythema or blanching of the skin
  - Absence of peripheral pain sensation can lead to skin trauma
  - Impairment of deep tendon and corneal reflexes

- **Hemophagocytic lymphohistiocytosis**
  - Non-malignant but life threatening disorder
  - Uncontrolled proliferation of activated lymphocytes and histiocytes leads to hypersecretion of inflammatory cytokines
  - Manifestations: prolonged fever, hepatosplenomegaly, cytopenias

- **Immunodeficiency**
  - Congenital immunodeficiencies such as immunoglobulin deficiencies or lymphocyte function abnormalities can present with persistent fevers or persistent infections
  - Persistent fevers with or without focal infections

- **Infantile cortical hyperostosis**
  - Inherited disease with persistent fevers, subperiosteal bone hyperplasia and swelling of overlying tissues
  - Symptoms can include irritability and tenderness over the affected regions
  - Leukocytosis, elevation of ESR and radiologic demonstration of periosteal involvement establish the diagnosis

- **Inflammatory bowel disease**
  - Fever may be more common than abdominal symptoms, especially in patient’s with Crohn’s disease
  - Should be suspected in patients with anemia, weight loss and an elevated ESR

- **Kawasaki disease**
  - Multisystem vasculitis of unknown etiology

- **Periodic fevers**
  - Two most common heritable periodic fever disorders in children are familial Mediterranean fever and hyperimmunoglobulin D syndrome
    - **FMF**: autosomal recessive disorder in individuals of Mediterranean descent with episodic fever and serosal inflammation
    - **Hyperimmunoglobulin D syndrome**: autosomal recessive disease with episodes of fever, skin eruptions, abdominal complaints and joint involvement and elevated serum IgD
    - **Cyclic neutropenia**: patients are prone to fever during periods of severe neutropenia, which occur at regular intervals of 15 to 35 days

**References**


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