Fever of Unknown Origin in Children

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Definition

- Fever >38.3°C rectal (37.8°C oral, 37.3 °C axillary)
- > 8 days
- No diagnosis after history and physical examination
- The required duration of fever ranged from five days to three weeks.

Causes of FUO

- FUO is usually caused by common disorders, often with an unusual presentation
- Most cases resolves without a diagnosis or develop characteristics that lead to a diagnosis
- FUO must be differentiated from sequential febrile illnesses which may be associated with new symptoms

Causes of FUO

- Infection(51%): viral, bacterial, mycobacterial, parasitic
 - Generalized
 - Localized
- Rheumatologic/ autoimmune disorders(9%)
- Malignancies(6%)
- Others

Viral- Epstein-Barr virus

- Three forms: pharyngeal, glandular, typhoidal
- Clinical clues: atypical lymphocytosis, mild elevation of liver enzymes, mild symptoms of EBV

Viral : CMV -induced mononucleosis

- Fever and strikingly severe malaise
- Rarely pharyngitis, tonsillitis, or significant splenomegaly
- Peripheral lymphocytosis with atypical lymphocytes, and mildly elevated liver enzymes

Viral :Hepatitis viruses

- Can cause FUO during prodromal phase of all viruses
- Elevated liver enzymes is present in all cases

Viral :Respiratory viruses

- Enteroviruses
- Adenovirus

Bacterial: Brucellosis

- Triad of fever, arthritis and splenomegaly is not present in all cases
- Exposure to animals or animal products
- Clinical suspicious in osteoarticular complaints, epididymo-orchitis, hepatosplenomegaly, mild elevation of liver enzymes, and lymphopenia

Bacterial: Salmonellosis & typhoid fever

- Transmission from infected humans or food products especially poultry and eggs
- Clinical suspicious in relative bradycardia
- Diagnosis with blood and stool cultures
- Widal test is not recommended

Mycobacteria: Extra-pulmonary TB

- Disseminated TB, or TB of the liver, peritoneum, pericardium, or genitourinary tract
- Can occur in children with negative chest radiography and tuberculin skin tests
- History of possible contacts

Mycobacteria: Disseminated BCG infection

- Criteria:
 - Fever and constitutional symptoms(weight loss, anorexia, sweeting, ..)
 - Involvemont of atleast 2 extra regional site(pulmonary, liver, spleen,)
- Exaggerated inflammation in the region of the injection

Parasitic: Malaria

- Typically paroxysm of chills and fever
- History of travel to endemicareas
- Usually splenomegaly is present
- Diagnosis by thin or thick smears of blood

Parasitic: Toxoplasmosis

- Exposure to soil or ingestion of foods contaminated with feline feces
- Mostly accompanied by cervical or supraclavicular lymphadenopathy
- Diagnosis by serology(IgM, rise of IgG)

Parasitic: Visceral leishmaniosis

- Classic findings: fever, hepato-splenomegaly, pancytopenia, hypoalbuminemia, hypergammaglobulinemia
- Mostly in nomades



Localized infections

Osteomyelitis and septic arthritis

- More commonly with osteomyelitis than with septic arthritis
- The pelvic bones, small bones, and flat bones are more frequently involved than long bones
- Diagnosis by magnetic resonance imaging, and radioisotopic bone scanning

Infective endocarditis

- Rare in infants but increases as children age
- Usually with a pre-existing cardiac lesion
- Do not always have positive blood cultures or a cardiac murmur,
- Associated findings ↓Hb, ↑ WBC, ↑ ESR
- Negative blood cultures in: previous antibiotic use, right-sided involvement, or unusual organisms

Intraabdominal abscess

- Liver, subphrenic, perinephric, and pelvic abscesses
- Patients may not have abdominal complaints
- Increased suspicion in history of prior intraabdominal disease, abdominal surgery, or vague abdominal pain
- Diagnosis by ultrasonography or CT of the abdomen

Upper respiratory tract infection

- Mastoiditis, sinusitis, otitis media, peritonsillar abscess have been reported
- It appears that localized complaints may be ignored as trivial

Urinary tract infection

Most common causes of FUO in children





Rheumatologic disease

Rheumatologic disease

- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Vasculitis (eg, polyarteritis nodosa)

Juvenile idiopathic arthritis

- Systemic presentation as high, spiking fevers, evanescent rash, and lymphadenopathy
- Arthritis may follow the development of fevers by months to years.
- Serologic tests are usually negative, and thus, JIA initially may be a diagnosis of exclusion

Malignancies



Malignancies

- Leukemia and lymphoma are the most common
- Other less common tumors include neuroblastoma, hepatoma, sarcoma, and atrial myxoma
- Usually have manifestations other than fever
- Bone pain that arise the child from the sleep



Other causes

Central nervous system dysfunction

- In children with severe brain damage or other CNS dysfunctions
- Altered thermoregulation
- Intermittent or recurrent elevated body temperatures
- Epilepsy-induced fever in some cases

Diabetes insipidus

- Dehydration induced fever
- Polyuria and polydipsia are difficult to appreciate during infancy
- Other features include weight loss, and decreased peripheral perfusion

Drug fever

- Allergic reaction to drugs
- Virtually any drug
- Any duration of drug consumption
- Any type of fever: low-grade or high and spiking fevers; continuous or intermittent.
- Typically disappear within 48-72 hrs of discontinuation
- Topical atropine can also cause fever
- Some drugs(phenothiazines, anticholinergic drugs, and epinephrine) impair thermoregulation

Factitious fever

- False report by a parent; or manipulation of temperature by rinsing the mouth with or dipping the thermometer into hot liquid
- Clues:
 - Absence of tachycardia and nonspecific symptoms of high fever
 - Rapid defervescence without diaphoresis
 - Failure of normal diurnal variation
 - Extreme hyperpyrexia
 - Discrepancies records and rectal T or RECORDS when someone is observing in the room
- Sometimes the injection of infective or foreign materials to produce fever(Munchausen syndrome or Munchausen syndrome by proxy)

Familial dysautonomia or Riley-Day syndrome

- Autosomal recessive disorder
- The majority from Ashkenazi Jewish parentage
- Autonomic and peripheral sensory nerve dysfunction results in defective temperature regulation
- Suggested features:
 - poor coordination of swallowing, excessive salivation, diminished tearing, excessive or diminished sweating, labile blood pressure, and erythema or blotchiness of the skin, sparse fungiform papillae of the tongue, Absence of peripheral pain sensation, impaired DTRs

Hemophagocytic lymphohistiocytosis

- Uncontrolled proliferation of activated lymphocytes and histiocytes leads to hemophagocytosis
- 2 forms: familial and reactive(infection, immunologic disorder, malignancy, or drugs)
- Typical findings: prolonged fever, hepatosplenomegaly, hyperferritinemia, and cytopenias
- Diagnosis (at least 5 of 8): fever, splenomegaly, bicytopenia, ↑ ferritine, ↑triglyceride / ↓ fibrinoge, hemophagocytosis IN BMA, ↓ NK cell activity, and ↑ soluble IL2-receptor

Inflammatory bowel disease

- Abdominal symptoms may be minimal especially in Crohn disease
- Suggestive findings: ↑ ESR, ↓ Hb, weight loss, failure of linear growth, or occult blood in the stool
- Diagnosis by Abdominal CT with contrast

Kawasaki disease

- In age < 6 mo with fever> 7 d and 1 ESR should be considered
- Typical findings may not appear until the 2 wk
- Typical findings may have occurred and resolved by the time of examination



Management of FUO

Indications for admission

- Ill-appearance
- Progressive symptoms
- Suspected Munchausen syndrome by proxy
- Need to procedures in the inpatient setting

Pace of the evaluations

- Quickly in ill-appearing, deteriorating clinically, or some chronic medical condition (eg, HIV, sickle cell disease, immune deficiency; CF; tracheostomy tube, cochlear implant)
- More deliberate in well children which sometimes resolves without explanation.

Evaluation of FUO

- The 1st step: verification of the height and duration of fever to diagnosis sequential febrile infections
- 2nd step: detailed history, physical examination, basic diagnostic tests
- 3rd step: additional testing targeted to clinical findings

Detailed history & physical examination

- Incomplete histories, overlooked physical findings, and failure to correctly interpret laboratory data were the main cause of delayed diagnosis
- The clinician must repeat the clinical assessment on multiple occasions

Detailed history & physical examination

- Obtain as much detail about the fever as possible
- It is important to ask, and ask again, about past or current abnormalities or complaints
- Ask, and ask again about the exposures: Medications, surgical procedures, Contact with infected or otherwise ill persons, animals, Travel, pica
- Even subtle abnormalities may be relevant

Basic tests for all patients

- CBC
- ESR
- Aerobic and anaerobic blood cultures: bacteremia, infective endocarditis, typhoid fever, or brucellosis
- Urinalysis and urine culture
- Chest radiograph
- TST & IGRAs
- Serum electrolytes, blood urea nitrogen (BUN), creatinine
- Hepatic aminotransferases
- Wright test
- HIV immunoassay
- Abdominal ultrasonography

Complete blood count

- Anemia: Malaria, tuberculosis, infective endocarditis, JIA, SLE, IBD
- Cytopenia: Leukemia, hemophagocytic lymphohistiocytosis, SLE,
- Leukocytosis/ bandemia: bacterial infection, JIA, drug fever
- Neutropenia: EBV, CMV, HIV; SLE; leukemia
- Atypical lymphocytes: Viral infection (eg, EBV, CMV),
- Lymphocytosis: EBV, toxoplasmosis

Complete blood count

- Lymphocytopenia Brucellosis, malaria, tuberculosis, typhoid fever, HIV, SLE
- Eosinophilia :Parasitic or fungal infection, allergic disorder, neoplasm, drug fever
- Thrombocytosis : JIA, Kawasaki disease, nonspecific marker of inflammation
- Thrombocytopenia : EBV, CMV, HIV, SLE

ESR or CRP

- Elevation of ESR and CRP: decrease the likelihood of factious fever
- Normal ESR and CRP: decrease the likelihood of infectious and inflammatory causes of FUO and may justify slowing the pace of the evaluation.
- Normal ESR and CRP do not exclude noninflammatory causes

Urinalysis

- Sterile pyuria: Kawasaki disease, adjacent intraabdominal infection, genitourinary tuberculosis
- Hematuria and/or proteinuria: SLE, infective endocarditis, leptospirosis
- Low specific gravity or osmolality: Diabetes insipidus

Chest radiograph

- Infiltrate: Pneumonia
- Lymphadenopathy: Tuberculosis, lymphoma
- Mediastinal mass: Leukemia, lymphoma, neurogenic tumor, rhabdomyosarcoma

Serum electrolytes, BUN, Cr

- Hypernatremia: diabetes insipidus or dehydration.
- Hyponatremia: leptospirosis or tularemia
- Elevated BUN and creatinine: renal impairment (eg, in SLE) or dehydration

Elevated hepatic aminotransferases

- Elevated hepatic aminotransferases :
 - Adenovirus
 - EBV
 - CMV
 - Brucellosis
 - JIA
 - Malignancy

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Additional targeted testing

- Suspected generalized infection : Brucellosis, Cat scratch disease, Leptospirosis, Malaria, Tuberculosis, Salmonellosis, Toxoplasmosis, Tularemia, Typhoid fever
- Children at risk for syphilis : serologic testing
- Cytopenias in ≥1 cell line: ANA, bone marrow aspirate and biopsy

Additional targeted testing

- Suspected endocarditis (CHD, murmur, petechiae), or laboratory findings (anemia, elevated ESR/CRP, positive blood culture) : multiple blood cultures, ECG & echocardiography
- Loose stools: S/E & S/C, Testing for Clostridium difficile infection
- Gastrointestinal complaints or failure to thrive: guaiac test(enteric infection, IBD, or vasculitis)

Additional targeted testing

- Abdominal masses: Abdominal CT Scan / MRI with contrast
- Bone tenderness: plain radiographs, MRI, Bone scan
- Age >5 yrs+ strong family history of rheumatologic disease: ANA, ophthalmologic examination
- Suspected IBD (↑ ESR or CRP, anorexia, weight loss, short stature, abdominal complaints): GI consult

Diagnostic interventions

- Discontinue medications :
 - Multiple medications discontinued individually
 - Resolution of fever within two half-lives of the drug supports the diagnosis of drug fever

Therapeutic trials

- NSAID in suspected JIA:
 - Resolution of fever supports the diagnosis
 - Response does not help to distinguish between infectious and noninfectious causes
- Empiric antimicrobials:
 - Only in suspected life-threatening infections: malaria, typhoid fever, disseminated tuberculosis
 - In others can mask or delay the diagnosis and interfere with isolation of an organism
- Empiric IVIG:
 - Suspected Kawasaki disease
 - Pretreatment serum sample for future testing

Subsequent evaluation

- Prepare a fever diary and request to return if new complaints
- If FUO resolves: not perform additional evaluation
- If the FUO persists: serial evaluations and additional diagnostic studies if new symptoms or signs