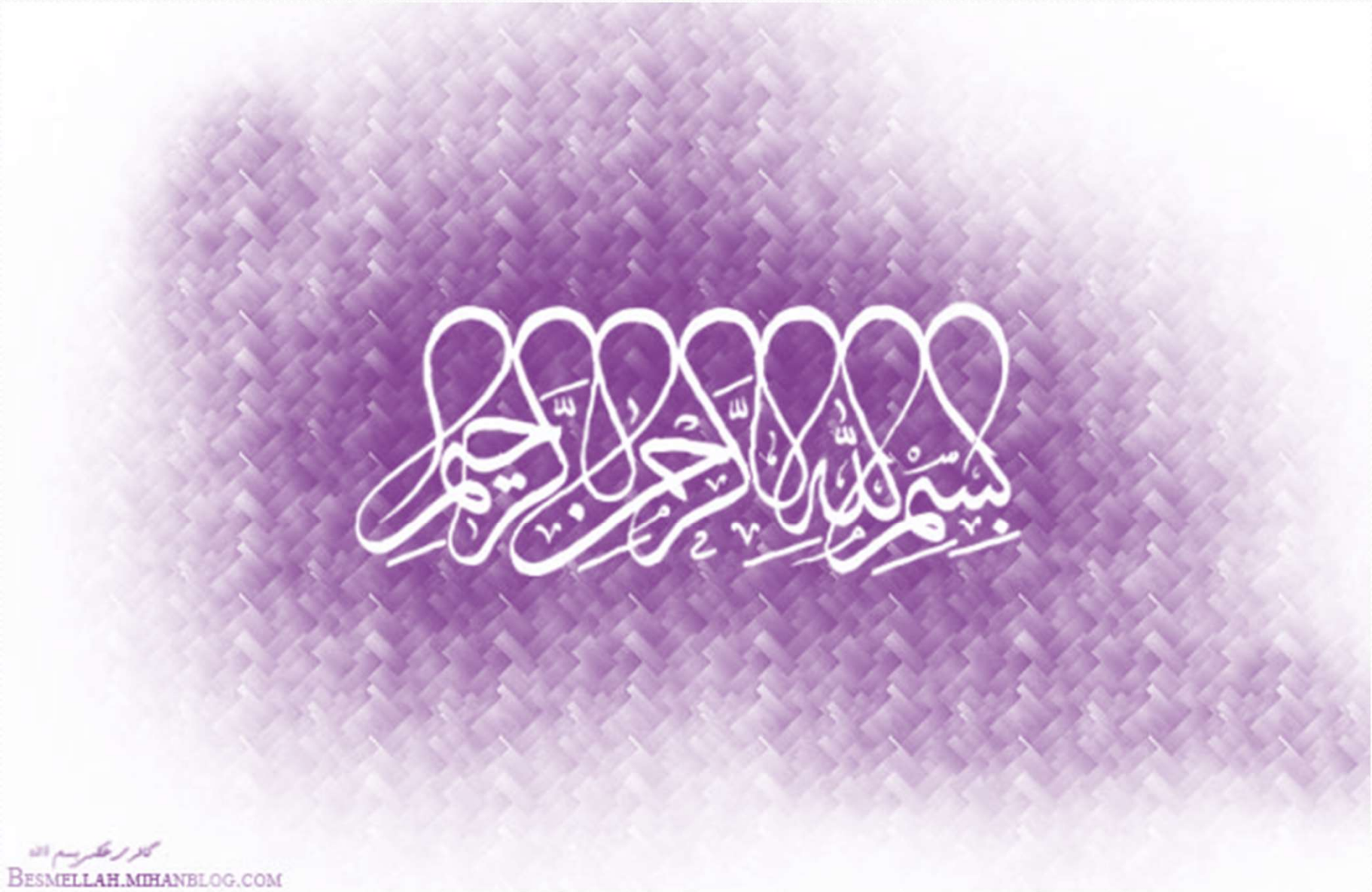
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Fever of Unknown Origin in Children

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Definition

- Fever >۳۸/۳ºC rectal (۳۷/۸ºC oral, ۳۷/۳ ºC axillary)
- > ۸ d.(۵-۲۱ d.)
- No diagnosis after history and physical examination

FUO

- Usually unusual presentation of common disorders
- Mostly resolves without diagnosis or develop new symptoms that lead to a diagnosis
- Must be differentiated from sequential febrile illnesses which may be associated with new symptoms

Main Causes of FUO

- Infection: ۵۱%
- Rheumatologic/ autoimmune disorders: ۹%
- Malignancies: ۶%
- Unknown: ۲۳%
- Others : ۱%

Infection ١

- Viral:
  ١. Infectious mononucleosis(EBV, CMV)
  ٢. Hepatitis viruses
  ٣. HIV
  ٤. Adenoviruses, Enteroviruses
- Bacterial:
  ١. Brucellosis
  ٢. Salmonellosis & typhoid fever
  ٣. Occult bacteremia
- Mycobacteria:
  ١. Extra-pulmonary TB
  ٢. Disseminated BCG infection

Infection ۲

- Parasitic
  ۱. Malaria
  ۲. Visceral leishmaniosis
  ۳. Toxoplasmosis
- Localized infections
  ۱. Abscesses
  ۲. UTI
  ۳. Osteomyelitis
  ۴. Mastoiditis, sinusitis, otitis media, peritonsillar abscess
  ۵. Infective endocarditis

Rheumatologic and autoimmune disorders

١. Juvenile idiopathic arthritis
٢. Inflammatory bowel disease
٣. Hemophagocytic lymphohistiocytosis (HLH)
٤. Kawasaki disease
٥. Systemic lupus erythematosus
٦. Vasculitis (eg, polyarteritis nodosa)

Hemophagocytic lymphohistiocytosis

- Uncontrolled proliferation of activated lymphocytes and histiocytes leads to hemophagocytosis
- ۲ forms: familial and reactive(infection, immunologic disorder, malignancy, or drugs)
- Typical findings: prolonged fever, hepatosplenomegaly, hyperferritinemia, and cytopenias
- Diagnosis (at least ۵ of ۸): fever, splenomegaly, bicytopenia, ↑ ferritine, ↑triglyceride / ↓ fibrinoge, hemophagocytosis in BMA, ↓ NK cell activity, and ↑ soluble IL۲-receptor

Malignancies

١. Leukemia
٢. Lymphoma
٣. Neuroblastoma
٤. Hepatoma
٥. Sarcoma
٦. Atrial myxoma
   - Other manifestations, Bone pain

Others

١. Central nervous system dysfunction
٢. Drug fever
٣. Factitious fever
٤. Diabetes insipidus
٥. Familial dysautonomia or Riley-Day syndrome

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

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 ۴۸-۷۲ 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/ 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
- 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

Evaluation of FUO

- ۱st step: verification of the height and duration of fever to diagnosis sequential febrile infections
- ۲nd step: detailed history, physical examination, basic diagnostic tests
- ۳rd 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

Additional targeted testing

- Abdominal masses: Abdominal CT Scan / MRI with contrast
- Bone tenderness: plain radiographs, MRI, Bone scan
- Age >۵ yrs+ strong family history of rheumatologic disease: ANA, ophthalmologic examination
- Suspected IBD (↑ ESR or CRP, anorexia, weight loss, short stature, abdominal complaints): GI consult

Additional targeted testing

- Suspected endocarditis (CHD, murmur, petechia), 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

- Suspected generalized infection : Brucellosis, Cat scratch disease, Leptospirosis, Malaria, Tuberculosis, Salmonellosis, Toxoplasmosis, Tularemia, Typhoid fever
- Children at risk for syphilis : serologic testing
- Cytopenias in ≥۱ cell line: ANA, bone marrow aspirate and biopsy

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


هر روز که نو می شود
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یعنی گامی به عقب نهاده ای
برگرفته از کتاب از یار آشنا سخن آشنا نوشته استاد سید علی موسوی