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Review Article

Fever of Unknown Origin in Children

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Summary:
Fever is a common symptom in children and fever of unknown origin (FUO) is not uncommon in paediatric age group. The FUO remains a challenging clinical problem and is an important cause of morbidity and mortality in children. These undifferentiated prolonged fevers need step-wise approach for diagnosis. Details and proper history taking, thorough serial physical examination, critical analysis of sign-symptoms diary and investigation reports are crucial to get a clue that led to the diagnosis. Though in some aspect more concerned with developing countries data, this article is based on reviewing of published papers from both developed and developing countries. Worldwide infection remains the most common cause of FUO in children, followed by collagen vascular diseases, neoplasm, miscellaneous diseases and undiagnosed illnesses. Indiscriminate use of antimicrobials and other medications may mask the real diagnosis. Awareness of primary-level healthcare providers about the cause and logical management approach of pediatric FUO is important for better outcome.

Introduction:
Fever is one of the most common reasons for which children need to visit a doctor. Although in majority of the cases in children, fever is a symptom of self-limited viral infection, in some cases, it could be a sign of a serious illness related to a life-threatening infection or malignancy. Rarely, the fever is prolonged or recurrent and the aetiology is not readily apparent. The differential diagnosis of these unexplained fevers is broad, and the evaluation of such children requires a step-wise approach.[1]

Fever and Fever of Unknown Origin (FUO)
Children are considered to have fever if their body temperature (axillary) is above 99.5°F.[2] American College of Emergency Physicians (ACEP) chooses a rectal temperature of >38◦C (100.4°F) as the most widely used definition of fever.[3]
Based on expert opinion and literature review, Marcy et al suggested that fever is the endogenous elevation of at least one measured body temperature of ≥38°C (100.4°F), regardless of the intrinsic and extrinsic factors- in other words, at any anatomic site, using any device, at any age, and under all environmental condition.[4]
Most children who present with fever have additional signs and symptoms that leads to a specific diagnosis. Fever without a source may need further evaluation that includes laboratory tests or imaging. Rarely, the fever is more prolonged, requires more intensive evaluation, and falls in the category of fever of unknown origin (FUO).[5]
The FUO concept in adults was introduced by Petersdorf and Beeson in 1961[6] but was not addressed in children until the 1970s. Some important articles about FUO were published previously, as retrospective case series and each used a different definition of fever on unknown origin (FUO).[7-11]

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Definition of FUO in children is still controversial. McClung as well as Lohr and Hendeley both defined pediatric FUO as an illness marked by 3 weeks of intermittent fever ≥39.0°C despite aggressive outpatient evaluation, or 1 week of intensive inpatient evaluation.[7]

More recent investigators have shortened the time requirement necessary for a febrile illness to qualify as a FUO. Pizzo defined PUO in children as a temperature ≥ 38.5°C on ≥4 occasions for at least 2 weeks.[8] Lorin and Feigin have defined FUO as a febrile illness of at least 8 days in duration in which no diagnosis is apparent after an initial evaluation either in the hospital or as an outpatient.[12] Recently, the definition has been altered to three visits without a diagnosis being reached in outpatients.[13]

Causes of FUO in children [14-22]

The causes of prolonged FUO may be classified into 5 categories: (1) infectious diseases, (2) collagen-vascular diseases, (3) neoplasms, (4) miscellaneous diseases and (5) undiagnosed illnesses.

1. Infection:

The common infections reported from the developing countries include Tuberculosis, Enteric Fever, Urinary Tract Infection (UTI), Malaria, Rickettsial Disease, Infectious mononucleosis, Cytomegalovirus, Hepatitis A, B, and C, Meningitis, Leishmaniasis, Bacterial Endocarditis, Abscess (Hepatic, Gluteal, Abdominal, Pelvic, Brain, Epidural, Dental, Paraspinal, Perinephric, Rectal, Subphrenic, Psoas), Septic Joint, Osteomyelitis, Pneumonia, Sinusitis, Brucellosis, Human immune deficiency virus.

2. Collagen vascular disease:

Juvenile idiopathic arthritis, systemic lupus erythematosus, Kawasaki disease, Atypical Kawasaki, Polyarteritis nodosa, Dermatomyositis, Rheumatic Fever, Behcet's disease, Vasculitis of unknown origin.

3. Neoplasms:

Leukaemia, Lymphoma, Neuroblastoma, Langerhans cell histiocytosis, Hemophagocytic Syndrome, Hepatocellular Carcinoma.

4. Miscellaneous Diseases:

Drug fever, Diabetes Insipidus, Periodic fever, Inflammatory bowel disease, Familial dysautonomia, Factitious fever, Kikuchi fujimoto disease, Addison disease, Pancreatitis, Thyrotoxicosis, Thyroiditis.

5. Undiagnosed illnesses.

Most of the undiagnosed FUO cases appear to be benign and many of them were found to resolve spontaneously without a confirmed cause. These cases possibly consist of prolonged viral syndromes or difficult-to-confirm atypical bacterial infections.

Among infectious causes, there is variations between developed and developing countries. In developing countries, common infectious causes include tuberculosis, typhoid fever, malaria, and Leishmaniasis. While in developed countries, common infectious causes include lyme disease, cat scratch disease, cytomegalovirus (CMV) infection and brucellosis. Similarly, the rate of vaccine preventable diseases is higher in developing compared to developed countries.

One study in Turkey found that second most common cause of FUO in children is immune deficiency diseases such as Di-George syndrome, immotile cilia syndrome, selective IgA deficiency and transient hypogammaglobulinemia in infancy, which is an unusual finding compared with other studies.

Geographical and socio-economic factors, age distribution and time of study are all known to influence the etiology of FUO in a given population. In addition, the native population, their characteristic traits and the flora and fauna also influence local disease patterns and epidemiology. Local referral patterns and hospital settings further modify the diagnosis. Study findings of FUO conducted in developed countries and those from developing countries are different, because of limited availability of expensive serological and other tests in later settings.

Evaluation of FUO:

A. History and physical examination:

Evaluation of FUO should be systematic and logically guided by history and physical examination findings. A thorough physical examination along with detailed history and a critical analysis of the laboratory tests already performed are important.

The first step in evaluating FUO is documentation of fever, because the perception of the reporting parents regarding fever often varies from the medical definition. It is useful to determine what the parent defines as fever and whether this varies from the medical definition of 38.0°C (100.4°F). Parents frequently report tactile or subjective fevers without actually measuring the patient's temperature with an instrument.

A detailed description of the patient's fever pattern as intermittent (tuberculosis, malaria), recurrent (periodic fever disorders), relapsing [Lymphoma, brucellosis, rat bite fever), remittent (typhoid, endocarditis, juvenile idiopathic

arthritis (JIA)], or sustained (pyogenic abscess, lobar pneumonia) can sometimes narrow the differential diagnosis.[23, 24] Information on the frequency and timing of fevers can be helpful in determining the fever curve and ability to document the fever in the medical setting. Though some researchers suggest that the pattern, magnitude and duration of fever are not useful in diagnosis of the causes of FUO.[25]

Fever can be the initial presentation of certain immunodeficiency syndromes, but many affected patients have a history of repeated infections, diarrhea, or abnormal physical findings, such as a rash. A history of atopy or autoimmune disease increases the likelihood of an autoimmune or rheumatologic cause. Furthermore, neutropenic fever in certain situations can be a medical emergency, and the presence of neutropenia may broaden the potential infectious sources.[26]

Travel history is critical in the evaluation of FUO (e.g., hilly area is endemic for malaria in Bangladesh). Exposure to animals, unusual foods, insect bites, and sick contacts are also important.

Drug history should also be asked, some antibiotics, anticonvulsants, neuroleptics, antiarrhythmic, vasodilators including others can cause prolonged fever. History of immunization against vaccine preventable diseases should be taken, although all vaccine does not have high protective value and vaccine failure is not uncommon. History of close contact with active tuberculosis is very important in Bangladesh and other developing countries in particular.[27]

One of the important aspects of evaluation for FUO is repeated history taking and encouraging the patient and family to report any new, different, or unusual signs or symptoms appeared. Serial physical examinations should be performed, and observation in a controlled inpatient setting may be beneficial because up to 25% of significant physical findings may be absent at the time of presentation.[23]

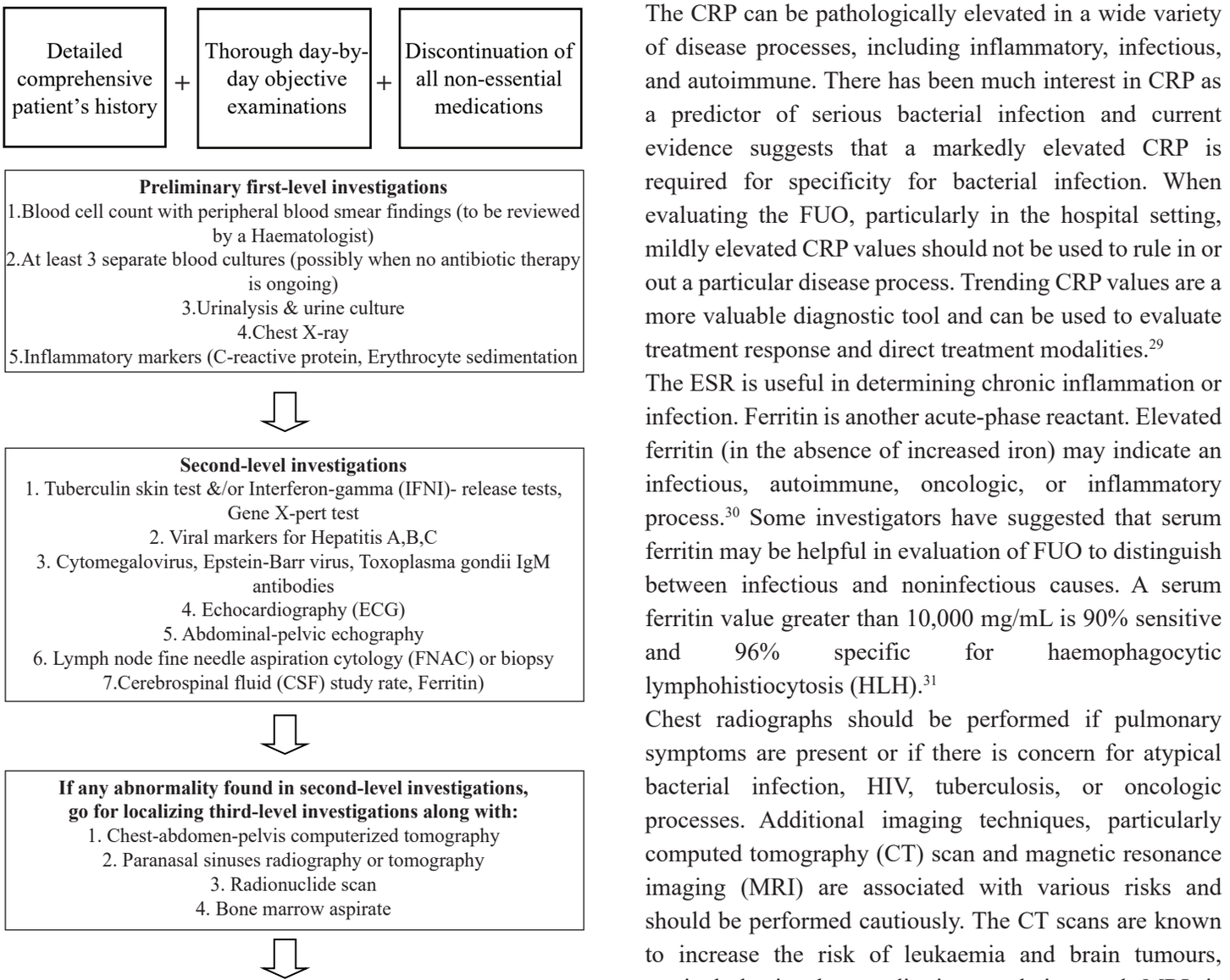
Table 1. Physical findings and associated Fever of Unknown Origin diagnoses[5]

Finding	Associated Illness
Hepatomegaly	Typhoid fever, malaria, lymphoma, leukemia, metastatic carcinoma, relapsing fever, granulomatous hepatitis, hemophagocytic lymphohistiocytosis (HLH), viral infections, brucellosis, bartonellosis, endocarditis
Splenomegaly	Leukemia, lymphoma, tuberculosis, typhoid fever, rickettsial disease, brucellosis, infective endocarditis, cytomegalovirus, HLH), Epstein-Barr virus, psittacosis, relapsing fever, Kikuchi-Fuijmoto disease
Liver edge tenderness	Liver abscess, Bartonellosis
Splenic abscess	Infective endocarditis, brucellosis, enteric fever
Murmur	Infective endocarditis, atrial myxoma
Relative bradycardia	Typhoid fever, malaria, leptospirosis, psittacosis, central fever, drug fever
Abnormal funduscopic examination findings	Miliary tuberculosis, toxoplasmosis, vasculitis
Conjunctivitis	Epstein-Barr virus, leptospirosis, Kawasaki disease (limbic sparing), tuberculosis, systemic lupus erythematosus, bartonellosis, chlamydial infection, histoplasmosis, tumor necrosis factor receptor associated periodic syndrome, familial cold autoinflammatory syndrome
Decreased pupillary constriction	Hypothalamic or autonomic dysfunction
Dry eyes	Systemic lupus, Familial dysautonomia, erythematosus, polyarteritis nodosa, Sjögren syndrome
Ischemic retinopathy	Polyarteritis nodosa
Periorbital edema	Tumor necrosis factor receptor-associated periodic syndrome
Subconjunctival hemorrhage	Endocarditis, trichinosis
Uveal tract involvement	Tuberculosis, juvenile idiopathic arthritis, toxoplasmosis, sarcoidosis, systemic lupus erythematosus
Lymphadenopathy	Lymphoma, tuberculosis, leukemia, bartonellosis, lymphogranuloma venereum, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, toxoplasmosis, juvenile idiopathic arthritis, brucellosis, Kikuchi-Fuijmoto disease, tularemia, viral infections, hyperimmunoglobulin D syndrome, familial cold autoinflammatory syndrome

B. Diagnostic Workup:

A number of basic laboratory studies may be used to determine the source of FUO. A complete blood cell count (CBC) with differential count and smear can suggest an infectious or oncologic cause. Blood and urine cultures are recommended, with the understanding that repeat cultures may be needed. If the patient has neurologic symptoms, cerebrospinal fluid (CSF) studies are also indicated. Whenever possible, cultures should be obtained before initiating antibiotics to avoid ambiguity and contamination of results. Abnormalities in serum electrolytes or liver enzymes may indicate viral, atypical bacterial or hematologic causes.[28] For all these purposes, the following flow-chart can be followed to evaluate the patient.

Flowchart of diagnostic workup for investigations of children with fever of unknown origin (FUO).[19]



Testing for acute-phase reactants, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin, is common in the evaluation of FUO. These test results are non-specific and not diagnostic of any particular disorder. On the other hand, elevated acute-phase reactants should encourage the physician to proceed with further appropriate evaluation. Although, normal acute-phase reactant results do not exclude serious causes of FUO.

The CRP can be pathologically elevated in a wide variety of disease processes, including inflammatory, infectious, and autoimmune. There has been much interest in CRP as a predictor of serious bacterial infection and current evidence suggests that a markedly elevated CRP is required for specificity for bacterial infection. When evaluating the FUO, particularly in the hospital setting, mildly elevated CRP values should not be used to rule in or out a particular disease process. Trending CRP values are a more valuable diagnostic tool and can be used to evaluate treatment response and direct treatment modalities.[29]

The ESR is useful in determining chronic inflammation or infection. Ferritin is another acute-phase reactant. Elevated ferritin (in the absence of increased iron) may indicate an infectious, autoimmune, oncologic, or inflammatory process.[30] Some investigators have suggested that serum ferritin may be helpful in evaluation of FUO to distinguish between infectious and noninfectious causes. A serum ferritin value greater than 10,000 mg/mL is 90% sensitive and 96% specific for haemophagocytic lymphohistiocytosis (HLH).[31]

Chest radiographs should be performed if pulmonary symptoms are present or if there is concern for atypical bacterial infection, HIV, tuberculosis, or oncologic processes. Additional imaging techniques, particularly computed tomography (CT) scan and magnetic resonance imaging (MRI) are associated with various risks and should be performed cautiously. The CT scans are known to increase the risk of leukaemia and brain tumours, particularly in the paediatric population and MRI is

time-consuming and often requires sedation in young children.[32]

Specific molecular testing for HIV, tuberculosis, or atypical bacterial pathogens and viral serologies are expensive and final results can be delayed days to weeks. These tests should be performed based on specific risk factors or suggestive physical findings.

A 2010 review also suggested a comprehensive metabolic profile including uric acid and lactate dehydrogenase and quantitative serum immunoglobulins.[33]

If fever persists and laboratory studies and imaging fail to reveal the underlying cause, invasive procedures may be necessary. Bone marrow biopsy can be performed to evaluate for oncologic or haematologic aetiologies. Thoracentesis, joint aspiration, or biopsies may also be indicated to obtain fluid or tissue for analysis.

Management:

The ultimate treatment of FUO is tailored to the underlying diagnosis.

Fever and infection in children are not synonymous, and antimicrobial agents should only be used when there is evidence of infection, with avoidance of empirical trials of medication. An exception may be the use of anti-tuberculous treatment in critically ill children with suspected disseminated tuberculosis. Empirical trials of other antimicrobial agents may be dangerous and can obscure the diagnosis of infective endocarditis, meningitis, para-meningeal infection, or osteomyelitis.

After a complete evaluation, antipyretics may be indicated to control fever associated with adverse symptoms.[34]

Outcome:

The outcome of FUO in children is determined by the underlying disease and to a lesser extent, by the rapidity of diagnosis. Diagnostic delay often results from failure to recognize helpful clues in a patient's history, although the mortality risk would seem uninfluenced, with the only exceptions of intra-abdominal abscesses, miliary tuberculosis, and disseminated fungal infections. However, when all diagnostic approaches are failing and the child's condition is stable, a careful ambulatory follow up might be a correct strategy to manage unresolved cases of FUO. For these paediatric patients, there is a general trend to consider their outcomes as favourable, with fever disappearing after 4-5 weeks and no sequels.[19]

Symptomatic treatment of FUO and significant organ/system dysfunction at the time of admission to the tertiary-care centre were the main risk factors leading to poor outcome. In contrast, careful, repeated clinical evaluation and the use of specific laboratory examinations or imaging, when new symptoms occur were found crucial for the favourable out-come of childhood FUO.[15]

In many cases, no diagnosis can be established and fever abates spontaneously. In as many as 25% of children in whom fever persists, the cause of the fever remains unclear, even after thorough evaluation.[34]

Conclusion:

Though fever is the most common presentation in childhood illness, in many cases, it becomes a difficult issue of handling, particularly, when it is prolonged in duration and undifferentiated in nature.

Even in today's high-tech era of medicine, FUO is one of those conditions in which the art of medicine is critical. Good communication between the clinician and the family and patient is often the key to success, and repeated history taking and physical examination by the old-fashioned diagnostician frequently becomes helpful.[35]

Education about the indiscriminate use of antibiotics for any febrile presentation and familiarizing primary care physicians about the common causes of FUO is important in improving the diagnosis and management of FUO in developing countries.

Further review is needed to determine the aetiology, mortality and overall outcomes associated with pediatric FUO particularly in Bangladesh context.

Conflict of interest: none declared.

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