

## Causes of Fever of unknown origin (FUO) in infants and children attending Assiut University Children's Hospital (AUCH)

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### ABSTRACT

**Background:** Fever of unknown origin (FUO) continues to be a diagnostic dilemma for pediatricians because it is often difficult to distinguish clinically between benign and potentially life-threatening causes. The term is best reserved for children with persistent fever  $>38^{\circ}\text{C}$  for which a cause could not be identified for more than 1 week.

**Aim of work:** to evaluate a four-stage investigative guideline for the detection of the causes of FUO among children.

**Methods:** 70 children aged between 6 weeks to 15 years with FUO were enrolled for this study. Graded investigations were done ranging from routine to advanced and/or specific investigations were performed after revision of detailed history and thorough examination.

**Results:** outpatient investigations were done in 8.6% of the cases. The duration of FUO in this study ranged from 12 days to 8 weeks. The causes of FUO were 31.4% bacterial infection and 11.4% viral infection including Covid-19 infection in 7.1% of them, herpes simplex, and glandular fever in 3.4% of them. ENT affection was present in 4.3%, and the cardiac cause was found in 4.3% of the cases. Malignancy was encountered in 10% of the cases. In 21.4% of the cases, the cause of FUO was not diagnosed. In 10% of the cases, connective tissue disease was detected, and auto-inflammatory disease was encountered in 7.1% of the cases.

**Conclusion:** not all cases of FUO should be admitted to a hospital, as some of them can be diagnosed and treated on an outpatient basis,

**Keywords:** causes, FUO, infants and children

### INTRODUCTION

Fever is defined as a central elevation of body temperature in response to stress or insult <sup>(1)</sup>.

It is one of the most common complaints in children and is the second reason for referring to a pediatrician. Based on history and physical examination, a specific cause is not found for about 5%-20% of the cases <sup>(1)</sup>.

Fever of unknown origin (FUO) is a diagnostic dilemma for pediatricians because it is often difficult to distinguish clinically between benign and potentially life-threatening causes. Pediatricians face the important challenge of not missing the diagnosis of a serious illness or uneasily treatable conditions that can result in increased morbidity. On the other hand, FUO can be an uncommon presentation of a common disease <sup>(2)</sup>.

The classification of FUO is best reserved for children with a temperature above  $38^{\circ}\text{C}$  for which a cause could not be identified or at least 7 days of evaluation. In some cases, the source of the fever could not be identified and fever becomes persistent and prolonged and can even progress to continue for months, especially in cases with immune deficiency or immune-mediated diseases.

However, it is generally accepted that a complete history and accurate physical examination with basic laboratory tests and empiric antibiotic therapy are initial steps in the workup of FUO. A chest x-ray is useful in reaching a diagnosis in a few cases of FUO with chronic infection e.g. tuberculosis (TB) <sup>(3)</sup>.

More advanced investigations e.g. CT scan or bone marrow aspiration may be needed for more serious causes of FUO e.g. malignant diseases. Recently PCR and immune globulins level as well as DNAase and HLA typing has been introduced for assessing connective tissue disorders <sup>(2)</sup>.

Diagnostic testing for FUO should be individualized and guided by abnormalities found on clinical examination and simple laboratory tests <sup>(4)</sup>.

In general, the causes of FUO in children are infection, rheumatologic (connective or autoimmune) diseases, auto inflammatory e.g. FMF, oncologic or GENETIC causes. Although oncologic disorders should be seriously considered, most children with malignancy do not have fever alone. The possibility of drug fever should be considered if the patient is receiving any drugs <sup>(2)</sup>.

The procedures to set FUO investigations must begin with routine laboratory tests e.g: CBC, CRP, ESR, and urine analysis. Tuberculin test and chest X-ray may be also indicated as first-line procedures.

Bacterial cultures may also be indicated. Serologic tests may be indicated in viral infections e.g: EPV, hepatitis virus, or COVID-19 infection if suspected from a positive PCR test. Invasive procedures may be indicated if malignancy is suspected e.g. bone marrow aspiration or CT scan for abdominal or orbital abscesses.

The Widal test may be helpful in cases with suspected typhoid as well as the Malta test for brucellosis. Echocardiography may be indicated if Kawasaki disease is suspected. MRI may be indicated

to localize a suspected tumor. Assessing the risk-benefit for the patient must be considered.

In general and after obtaining the necessary tests and results of investigations, antipyretics should be started to control fever to avoid febrile convulsions that may occur in young children (< 6 years) in these cases.

**PATIENT AND METHODS**

This was a prospective, descriptive study that was done for 70 children aged between 6weeks to 15 years with FUO. Graded investigations were done ranging from routine to advanced and/or specific investigations were performed after revision of detailed history and thorough examination.

The study was done in assiut University Children Hospital (AUCH) 2020\_ 2021.

**Inclusion criteria**

All patients fulfilling the diagnostic criteria of FUO cases attending AUCH during one year of study.

**Exclusion criteria**

Patients below one month and above 18 years.

**Ethical Approval:**

The study was approved by the Ethics Board of Assiut University and informed written consent was taken from each participant in the study or their guardians. This work was carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The following investigation algorithm is suggested by Gündeşlioğlu *et al.* (5) Figure (1).

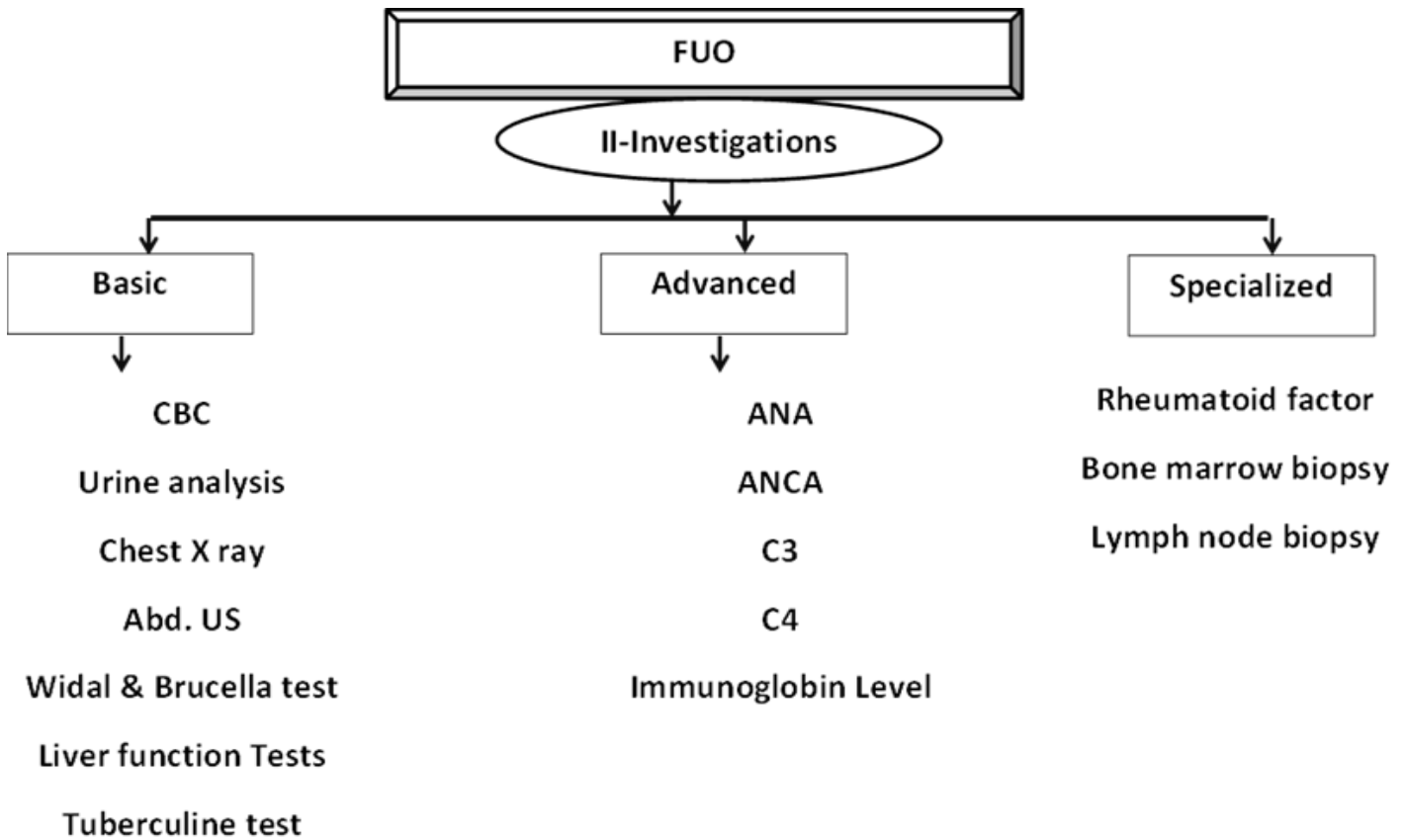


Figure (1): Algorithm for investigations in FUO

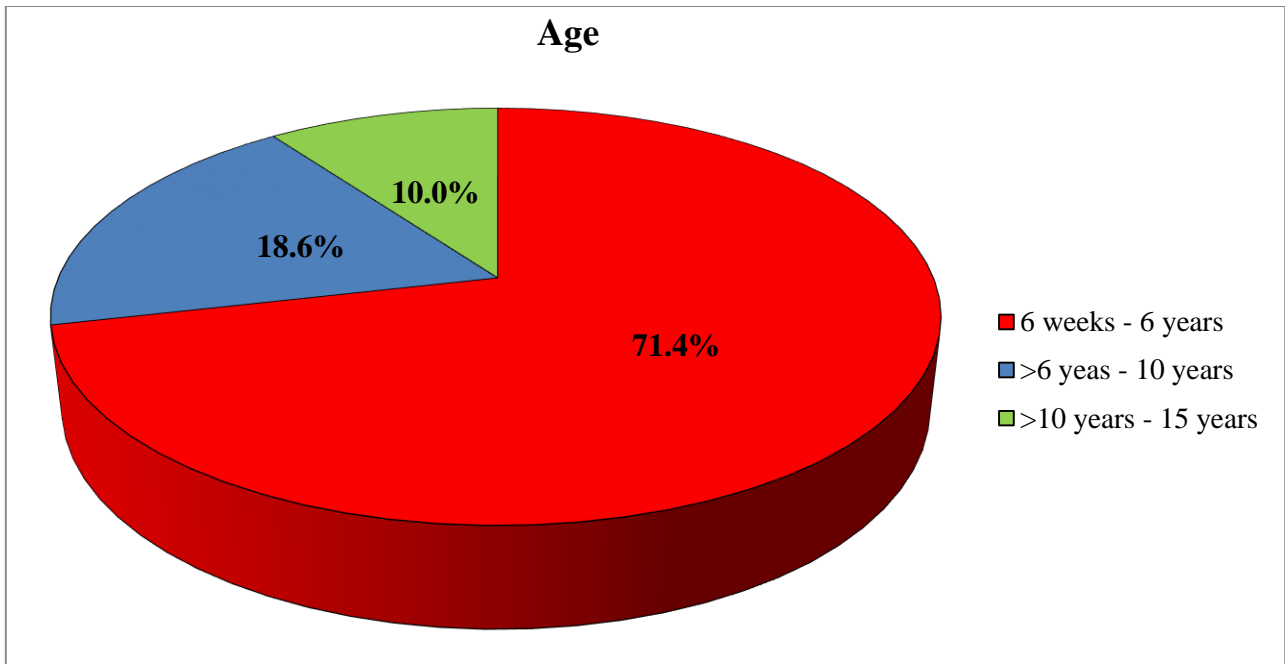
**Statistical analysis**

Analysis of data was done using a statistical program for the social science version 22 (SPSS Inc., Chicago, IL, USA). Qualitative variables were described as numbers and percentages.

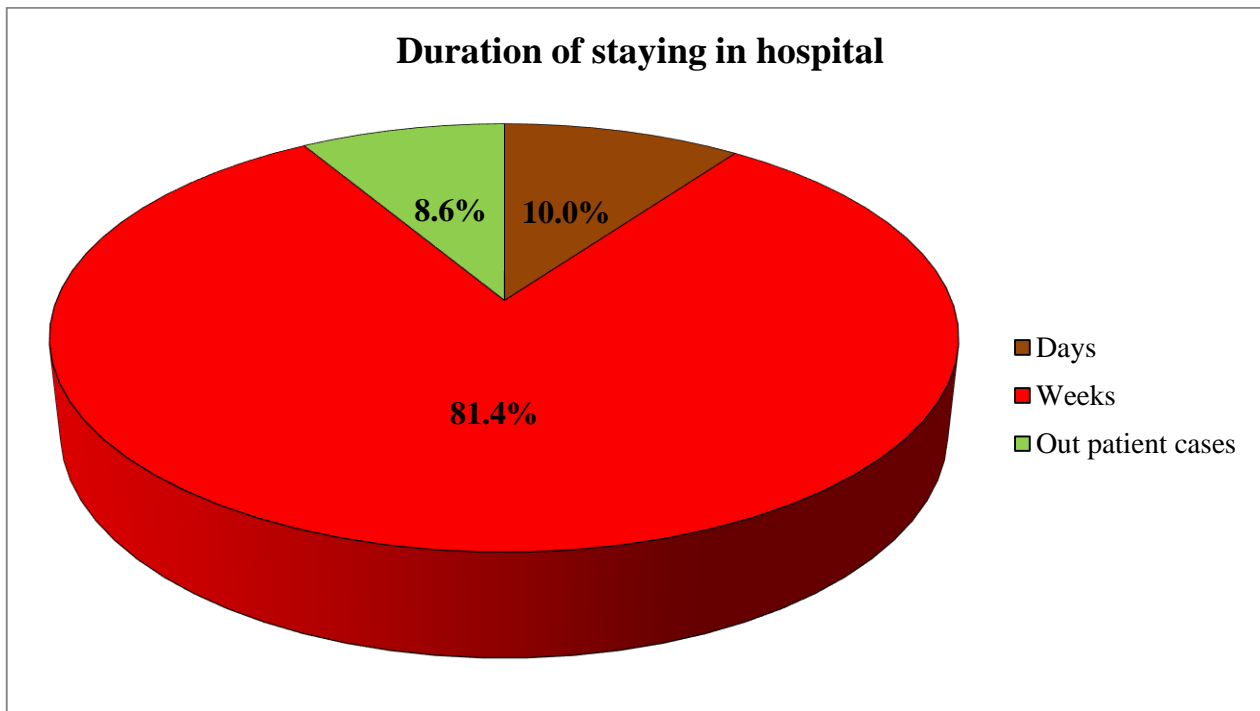
**RESULTS**

In 71.4% of cases, the ages ranged from 6 weeks to 6 years (**Figure 2**).

Outpatient management (diagnosis and treatment) was done in 8.6% of cases (**Figure 3**). Infection whether bacteria or viral was present in 31.4% + 11.4% of the cases [42.8%] (**figure 4**). Both ENT and cardiac cases were predisposed to and/or following upper respiratory tract infection in (8.6%)of the cases. Most of the cases in this study (71.4%) were therefore either due to infection or preceded by an upper respiratory tract infection (**figure 4**).



**Figure (2)** shows the age distribution of fever of unknown origin (FUO) cases studied.



**Figure (3)** shows the percentage of outpatients and the duration of their stay in the hospital in the cases of fever of unknown origin (FUO) studied.

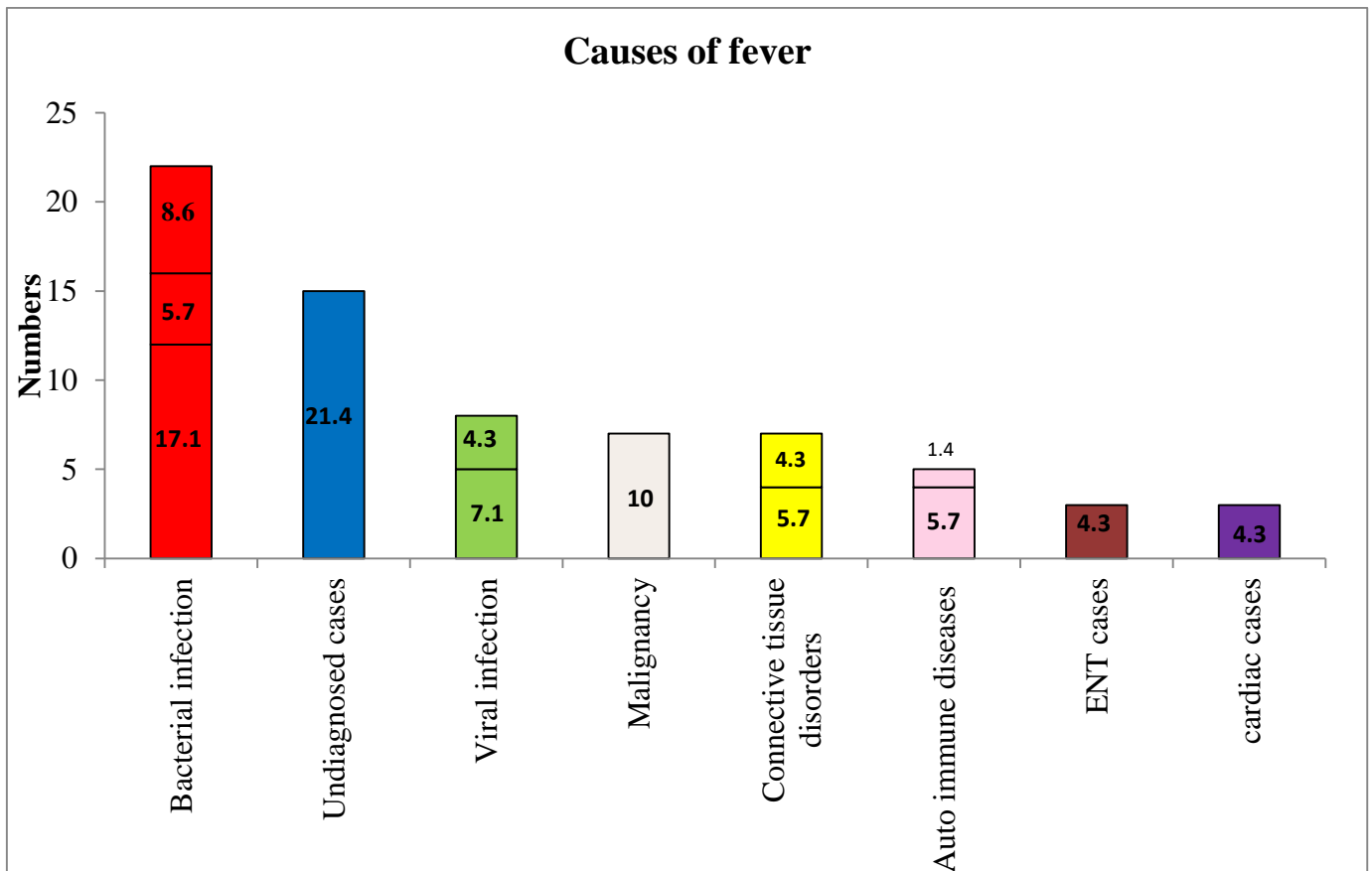


Figure (4) shows the distribution of the causes of fever in FUO cases studied.

## DISCUSSION

The finding in the present study is interesting where FUO is present in children aged less than 6 years whether with infection or immune-mediated diseases preceded by an upper respiratory tract infection as in cases with ENT affection and cardiac diseases or even with immune-mediated diseases. Although infection as a cause of FUO is in agreement with previous investigators <sup>(6)</sup>.

Yet our finding in the present series is at variance with authors with recent investigators <sup>(2,7)</sup> as our finding is that while they stated that immune-based FUO cases were encountered in their cases aged over 6 years; in the present study immune-mediated cause of FUO was present in cases less than 6 years of age (Figures 2& 4).

This is more obvious by studying the long staying in the hospital that was present in these young cases (Figure 3).

One may think that overcrowding and lack of good ventilation, as well as the more frequent marriage between cousins and relatives, is more common in upper Egypt and may be the underlying cause of this reference; so both environmental and hereditary causes are prevalent <sup>(4,6-8)</sup>.

The presence of malignancy as a cause of FUO in 10% of the cases in the present study is in agreement with <sup>(6)</sup>. Cases with malignancy were referred to the

oncology hospital for further advanced investigations and treatment in the present series.

The used algorithm in this study is satisfactory and can be recommended for use in the diagnosis of FUO in children.

## CONCLUSION

Immune-mediated FUO is now increasing at a younger age presenting with FUO, needing admission for a longer stay inside the hospital. A fact that can be managed with better housing and cleanliness of the environment as well as health education and decrease marriage among relatives.

Decreasing hospital admission indications for those with FUO children with warning signs such as weight loss, anorexia, pallor, skin rash as with vasculitis, arthritis, generalized lymphadenopathy, hepatosplenomegaly or bone pain with tenderness on the sternum as well as a positive family history of a similar condition. Do not admit to in-patient hospitalization of recurrent fever and not FUO where attacks last only for a few days with periods of cure in between.

## RECOMMENDATIONS

One must determine whether the fever is recurrent or FUO. Do not admit recurrent fever unless associated with systemic manifestations e.g.: rash,

arthritis, edema, or loss of weight. Only admit FUO with the recent definition being fever more than eight days to three weeks. Routine investigations can be done in the outpatient clinic and only admit cases not diagnosed by routine investigations and needing investigations done only inside the hospital. A positive family history of connective tissue disease or immune-mediated disease should be admitted to the hospital.

#### DECLARATIONS

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- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of Interest:** The authors declare no conflicts of interest regarding the publication of this paper.

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