

## Original Research

### Fever of Unknown Origin - Different Centuries, Different Patterns

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# Equal contribution

#### Abstract

**Background:** Imaging techniques used in the last decades, and reported changes in various disease prevalence, may have dramatically influenced causes of Fever of Unknown Origin (FUO).

**Objectives:** Our study's objectives were to identify changes in prevalence and etiologies of FUO, since our previous study two decades ago, to clarify the most beneficial diagnostic strategies, and to investigate the long-term outcomes of undiagnosed and diagnosed patients.

**Methods:** Medical files with "fever" as a cause for admission and at least one-week hospitalization were evaluated. Patients were screened based on Petersdorf's classic criteria. An interview was performed three months to twelve years after hospitalization.

**Results:** 3691 patients fit our primary selection criteria in 2004-2016; 141 patients fit Petersdorf's criteria for FUO. The most common cause of FUO was infectious disease (39%), mainly bacterial (29%), though decreased from our previous study (39% vs 55%). There were dramatic increases in the incidence of malignancy (19% vs 7.9%) and inflammatory (20% vs 2%) etiologies and less undiagnosed cases (22% vs 32.7%). Weakness and weight loss were the most common co-complaints (80% all coexisted). Elevated ESR (97%), elevated CRP (95%) and anemia (80%), were the most common pathologic laboratory examinations found. Abdominal CT,

blood cultures and serology proved to be the most valuable diagnostic tests. Long-term follow up interviews revealed that a final diagnosis was often reached during the patients' next admission (20% out of 70%). 2% of patients died during the feverish episode and 34% died three months to twelve years after the episode

**Conclusions:** Infections (mainly bacterial) remain the most common cause for FUO in southern Israel in the 21st century; although there is a remarkable increase in the rate of vasculitis and malignancy. When PET is not available, a thorough clinical examination including appropriate laboratory and imaging examination, as well as precise history taking are essential. Blood cultures and abdominal CT are the most useful diagnostic tests. Most undiagnosed cases resolved within days of discharge or are diagnosed in a following admission

**Keywords:** Aetiology; Fever of unknown origin; Infections; Malignancy; Undiagnosed fever

#### Introduction

Fever of Unknown Origin (FUO) is a classic medical phenomenon that is challenging for internal medicine physicians. In 1991, Durack and Street recommended differentiating between four classes of FUO: classical, nosocomial, neutropenic and HIV-associated [1]. They proposed a minimum diagnostic evaluation of three days in-hospital or three outpatient visits in order to allow for the time needed for incubating blood cultures and tuberculosis skin test to return positive. The newer definition is broader, including one week of an intelligent and invasive ambulatory investigation. An enormous change in the etiologies has occurred in the last several decades, most likely due to increasingly useful diagnostic technologies, both invasive and noninvasive imaging such as MRI, PET and others [2,3]. The most common etiologies are infectious, followed by malignancies and autoimmune diseases, and 7%-40% of the cases remain undiagnosed [4-7]. Surprisingly, 21st century European studies show that the rate of undiagnosed patients remains high, with 30-50% of patients undiagnosed despite extensive evaluation [8-10]. Our previous "FUO study", published sixteen years ago, found infectious diseases to be the most common cause of FUO in two rural hospitals in Israel [11]. A recent rise in patients with autoimmune related FUO, as well as the high prevalence (30%) of "undiagnosed cases" (similar to other previous studies, 10-40%) led us to conduct the current investigation through patient interviews performed months to years later [3-5]. Newer tools such as PET examination were found valuable in revealing both malignancy and vasculitis [8].

#### Patients and Methods

In order to design the current study, we relied on the experience of our previous study, and on a pilot study of a few hundred current medical files, in order to estimate the number of medical files and hence the number of years that should be checked in order not to miss any case of FUO. Based on this, we selected all medical files with fever as one of the causes for admission with a mandatory second basic requirement of hospitalization for at least one week, in order to include all patients with "FUO".

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### Inclusion criteria

- Fever persisting 3 weeks or more with at least 2 measurements of 38.3 C
- Hospitalization duration of one week or more
- No known immune deficiency
- Age >18 year
- Patient with preserved cognition

### Exclusion criteria

- Age <18 years
- Patients with dementia

Our study was a dynamic retrospective cohort study, with an interview conducted by a resident physician three months to twelve years after the hospitalization, regarding the patient’s prognosis and outcome including the details of final diagnosis (in the same hospital or another, as well as the timing of the final diagnosis and the timing of symptoms disappearance). A resident physician examined the medical files in order to reveal all cases compatible with the definition “FUO”. Since “FUO” is not a valid item in International Classification of Diseases-9 (ICD-9), intensive work was done to identify the most reliable and efficient way to uncover all the eligible patients. Our current standards were designed to avoid missing any “FUO” patients. The study was authorized by Institutional Review Board.

### Statistical analysis

The eligibility and classification of “FUO” syndrome were determined according to the original record of each item in the medical history and an examination of the database. All statistical analyses were performed with the statistical package for the social sciences (SPSS) VER.17 (SPSSCHICAGOIL). Statistical significance was assessed using ANOVA test. P values < .05 were considered to be statistically significant. All information was computed to excel and was estimated by a statistician.

## Results

### Demographics

141 medical files were found matching the diagnosis “FUO”, in concordance with our previous study, 55% were males. The average age was 58. The prevalence of undiagnosed patients decreased since our previous study (22% versus 32%) but with no statistical significance, p=.063 (Table 1). Infectious disease was found to be the most common cause of FUO with 39% due to bacterial disease. Pneumonia (defined by chest x-ray, acute phase reactants and typical clinic and specific pathogen in blood culture or sputum culture), abdominal abscess and endocarditis were the most prevalent bacterial infections. Infectious causes for FUO were much more common than malignancy and vasculitis/inflammatory disease. The prevalence of both malignant diseases (19% vs 7.9%) and autoimmune diseases (20% vs 2%) increased significantly since the last study. Temporal arteritis was the most common autoimmune disease found, followed by Still’s disease.

### Symptoms

The most common symptoms in addition to the fever were weakness (38%), weight loss (19%) and cough (18%) (Table 2).

Diagnosis	1978-1998 (%)	2004-2016 (%)	P value
Cases of FUO	101 (10%)	141 (3.4%)	0.013
Inflammatory/autoimmune dis.	2 (2%)	28 (20%)	< 0.001
Temporal arteritis	-	5 (4%)	
Polymyalgia rheumatica	-	3 (2%)	
Still's disease	-	2 (1%)	
Vasculitis	-	4 (3%)	
Sarcoidosis	-	2 (1%)	
SLE	-	1 (1%)	
Other Inflammatory/autoimmune	-	11 (8%)	
Infections	55 (54.4%)	55 (39%)	0.004
Rickettsial diseases	6 (5.9%)	2 (1%)	0.052
Bacterial	39 (38.7%)	40 (28%)	0.101
Pneumonia	2 (2%)	9 (6%)	0.104
Osteomyelitis	3 (3%)	1 (1%)	0.173
UTI	4 (4%)	3 (2%)	0.402
Wound infection	3 (3%)	2 (1%)	0.403
Other bacterial infections	0	10 (7%)	0.006
Viral	13 (12.9%)	15 (11%)	0.741
HIV	0	3 (2%)	0.14
Malignancy	8 (7.9%)	27 (19%)	0.014
Hematologic malignancy	-	18 (13%)	
Solid malignancy	-	9 (6%)	
Undiagnosed	33 (32.7%)	31 (22%)	0.063

**Table 1:** Etiologies of FUO.

Comparison of the two groups has been performed using Chi-square test with Yates’ correction (GraphPad Software, Inc, La Jolla, CA, USA).

Symptoms	Percentage	No. pts
Weakness	38%	54
Weight loss	19%	27
Cough	18%	26
Abdominal pain	15%	21
Asymptomatic	14%	20
Headache	13%	18
Muscular pain	10%	14
Rash	8%	11
Vomiting	7%	10
Diarrhea	6%	8
Chest pain	6%	8
Arthralgia	6%	9

**Table 2:** Symptoms.

### Diagnostic tests and imaging

Blood culture was the most commonly performed diagnostic laboratory test (obtained in all patients). An average of 4.8 blood cultures were taken, with a positive diagnostic result in 15%. Chest X-ray was the most common imaging test performed (all patients) followed by abdominal (69%) and chest CT (62%), and transthoracic cardiac echocardiography (68%). Leukocyte scan was performed only in seven patients and was diagnostic only in one. Acute phase reactants

when taken were elevated in 97% (ESR) and 95% (CRP) of the cases. Liver function disturbances were less commonly taken (53%) (Table 3).

Exams Significant for Diagnosis	Significant Diagnoses of Defined Cases	Number of Cases
Known/defined diagnosis	66%	93
Other	42%	39
Other biopsy	24%	22
Abdominal CT	18%	17
Blood cultures	15%	14
Serology	15%	14
Chest CT	8%	7
Based on other clinical criteria	8%	7
Cases with more than 1		5
TTE	2%	2
TEE	2%	2
Abdominal US	1%	1
Bone scan	1%	1
Leukocyte scan		0

Table 3: Significant diagnostic tests performed.

### Duration of fever/hospitalization

The average duration of hospitalization was 14 days. The average duration of fever prior to hospitalization was 26 days and the average total duration of fever was 31 days (Table 4).

Duration of Hospitalization		
7 days <	20	14%
days 7-14	69	49%
days 14-21	31	22%
days 21-28	17	12%
28 days >	4	3%
Total	141	100%
Average duration = 14 days hospital		
Duration of Fever Until Hospitalization		
1 week <	27	19%
weeks 1-2	30	21%
weeks 2-3	25	18%
weeks 3-4	31	22%
months 1-3	25	18%
3 months >	3	2%
Total	141	100%
Until fever duration Average days 26: hospitalization until fever of duration medium days 21: hospitalization		
Total Duration of Fever		
month < 1	74	52%
months 1-2	51	36%
months 2-3	8	6%
3 months >	8	6%
Total	141	100%
days 37 fever of duration Average days 31 fever of duration Median		

Table 4: Fever and Hospitalization timeline.

### Prognosis

An interview was conducted three months to twelve years after “FUO admission” with 79% of the patients. Only 3 patients (2%) died during their hospitalization with FUO, but 22 patients (17%) were found to die within the upcoming twelve years.

### Discussion

We found a significant increase (thrice) in the number of patients with one week of fever or more during hospitalization, especially considering the fact that the present study is based on one hospital’s data, versus two similar hospitals included in the previous study. In addition, we found an increase in the number of patients admitted with a diagnosis of FUO. This finding is somehow surprising because of the increasing availability of imaging and laboratory diagnostic tools to family physicians. This increase in prevalence of FUO is unique, as we did not find such a phenomenon in other studies and may be due to a more appropriate methodology in the current study. It certainly means that even nowadays, “FUO” is not a vanishing disease.

### Age of patients

Among other studies published in medical literature regarding FUO, the mean age of the patients in our study was comparable to West European and American literature with an average age of 58-60 years old [3-10]. Medical literature of developing countries (Mediterranean) reports a younger average age ranging from around 30 years old in Egypt [12,13], 41.3 years old in Saudi Arabia, and 49.9 years old in Iran [14,15]. This is most likely due to a younger population of patients in developing countries and a shorter life expectancy in these countries.

### Etiologies

Infection was the main cause of FUO in our study, similar to our previous study and to most FUO studies [11,3-14]. In contrast to other studies in the Mediterranean and developing countries [11-14], in which tuberculosis was the most common infectious cause of FUO, TB was not found in our study to be a significant cause of FUO (or cause of FUO at all) due to an efficient public health system and a well-known dramatic decline in the prevalence of TB in Israel. The incidence rate of TB in 2016 was 2.89 per 100,000 people, less than one third the rate in 1998 [16]. A significant decline in the prevalence of infectious disease was seen in the present study compared to our previous one. Public health efforts, improved hygiene and improved immunization may be the cause for the decrease in the prevalence of infections among FUO patients. A dual increase seen in both inflammatory and malignant diseases may relate to the wide availability of ultrasonography, CT, MRI, radionuclide scanning, and positron emission tomography scanning. 22% of FUO patients remained undiagnosed, similar to what was found in other western studies [2-4], but this is a remarkable and almost significant decline compared to our previous study in which 32.7% of FUO patients remained undiagnosed [11]. Surprisingly, studies performed in developing countries show a lower prevalence of undiagnosed patients [12-15], than in developed countries [2-4], notable fact we find difficult to explain. This may be due to the dominance of rare infections in developing countries, such as TB, Brucella and various others, which are prevalent in those areas, but uncommon elsewhere; TB, Brucella and typhoid are seen commonly in India [17]. Visceral leishmaniasis is seen in Macedonia [18].

## Evaluation

Most physicians start evaluation with thorough history taking, physical examination and a panel of standardized tests such as chest x ray, blood cultures, CBC, and renal and liver functions, to rule out common conditions. Recent studies have revealed that the proportion of undiagnosed FUO cases have paradoxically increased over time, due to improved diagnostic technique. Improved techniques make it easier to diagnose certain diseases earlier before the patient meets criteria for FUO, which leaves more complicated cases for “FUO” diagnoses [18]. The impressive reduction in the prevalence of both infectious disease and undiagnosed patients in our two studies was correlated with increases in neoplastic and autoimmune/inflammatory causes, compared to our previous study (though not statistically significant). These increases, especially the latter, are well described in recent medical literature [2]. These changes might be attributed to the improvement in serological and immunological diagnostic tests [18]. New imaging techniques such as PET-CT, MRI and modern isotopes scans, likely contribute to an earlier diagnosis of malignancy [19].

Radionuclide imaging such as indium and gallium scans have been used for years as a second line evaluation of FUO with moderate success. Labeled leukocytes imaging accurately localizes infection but is not useful in a case of malignancy or inflammatory disease [20]. However, FDG Positron Emission Tomography (PET) and PET/CT have rapidly assumed an increasingly important role in the diagnostic workup of patients with FUO. FDG-PET/CT seem to be a sensitive diagnostic technique that facilitates anatomic localization of focally increased FDG uptake, thereby guiding further tests to reach a final diagnosis [19,20]. Because the Barzilai Medical Center has no PET scan, only one of the patients underwent ambulatory PET-CT, which was diagnostic, showing recurrence of islet cell pancreatic adenocarcinoma. Six gallium scan examinations had no influence on the evaluation. We now send more patients for ambulatory FDP-PET SCAN for earlier stages of FUO evaluation. Several diagnostic approaches with a staged diagnostic protocol have been published [3,7]. After an intensive history taking and a good physical examination, a chest x ray is usually performed with laboratory examinations such as C Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), CBC, liver and kidney functions, and at least 2-3 blood cultures. We observe fever and pulse, looking for potential diagnostic clues [3,6,7]. If the fever continues after 3-4 days of hospitalization with no diagnostic progress, we continue a series of more intensive blood tests such as immunoelectrophoresis, ferritin, infectious and rheumatologic serology, and abdominal US (occasionally in the first stage), CT of the abdomen and the chest, cardiac transthoracic echocardiography (TTE), etc [18,19]. Our third diagnostic phase is guided by the results found in the second phase and includes isotope scans, colonoscopy and bone marrow or liver and temporal artery biopsies when necessary. Our evaluation included transthoracic echocardiography in 68% and transesophageal echocardiography of the heart in 13% of all patients with two main causes of high clinical suspicion or suspicious artificial valve, which decreases the reliability of TTE. Overall, 4% of both echocardiography of the heart were diagnostic.

Technetium or Indium scans, as well as gallium scans, are also recommended for FUO evaluation in the literature [18-20]. Gallium scans of bones with indium or leukocytes, were performed in 19% of patients, but according to the literature, were found inferior to PET-SCAN. Regarding empiric liver or bone marrow biopsy, it is clear

that a biopsy should be performed in the case of a suspicious solitary lesion in the liver or the lung, or an enlarged lymph node. There seems to be a place for empiric bone marrow and liver biopsy as well as, with no hepatic SOL (Space Occupying Lesion), but just liver functions disturbances. De Kleijn, et al. declared that many patients with FUO had nonspecific anemia and disturbed liver chemistry [3]. Without other more specific Primary Diagnostic Clues (PDCs), the likelihood of reaching a diagnosis with Bone Marrow Biopsy or Liver Needle Biopsy was null in the first and low in the second phase. Hot et al found Bone Marrow Biopsy to be a useful technique in FUO diagnosis with a diagnostic yield of 23.7% [21]. We found an overall positive yield of all biopsies (24%); only three of them were bone marrow biopsies. Bone marrow biopsy is an even more useful procedure in the diagnosis of fever with advanced HIV disease, particularly in areas where tuberculosis and leishmaniasis are prevalent [22]. Another approach to FUO is the therapeutic approach [23], which is generally not recommended in patients with prolonged fever because it may delay diagnosis. However certain therapies such as antibiotic use in suspected endocarditis, anti-TB drugs in suspected TB, and steroids in temporal arteritis with impending blindness, can be beneficial in a symptomatic patient. According to the response, these may be “diagnostic” when both fever due to malignancy and fever due to infectious cause are suspected. This therapeutic approach lacks sufficient sensitivity, and was hardly tried in our study except for a few unique cases.

## Laboratory tests

Anemia (at least mild) was found in 80% of patients (among 100% of patients with performed CBC). This high prevalence of anemia among all four diagnostic groups has not been previously described in western literature, though most malignancies and inflammatory diseases may be correlated with anemia. Naito et al. investigated the use of acute phase reactants as clinical clues [10]. They failed to use high ESR (>100) as marker of Polymyalgia Rheumatica, Tuberculosis, Multiple Myeloma or osteomyelitis. Precalcitonin, a popular acute phase reactant in Japan, has some advantage over C Reactive Protein, but failed to differentiate bacterial infections from other etiologies. CRP and ESR, although not found in all cases (ESR was checked in 30% of patients and CRP IN 57%), were elevated in almost all patients checked.

## Prognosis

Only three patients (2%) died during their hospitalization for FUO. But 22 patients (17%) died within the upcoming twelve years due to basic disease, usually malignancy. 12-35% of patients were reported to die from underlying diseases in classical FUO. Modern studies found a decline in mortality in the last decades with an average of 6% mortality following hospitalization, with a 5 year and a 6 month follow up period in the Netherlands and Belgium respectively [23,24]. Our study parallels others with a low prevalence of mortality (2%) in current hospitalization with FUO, but a higher long-term mortality (34%). We note however that our data was recorded over a much longer period of time (one month-twelve years). Half of the mortality was due to the basic disease and the other half, likely to advanced age.

## Long-term follow-up

Most of the patients (79%) answered the questionnaire. Among those patients that were not diagnosed during current hospitalization,

diagnosis was found within a short time of re-hospitalization in our hospital (7%) or another hospital in which the patient was admitted (6%), or in further ambulatory evaluation. In some patients, the fever disappeared spontaneously within a few days (28%).

### Limitations of the study

This is a retrospective study of one medical center and therefore the results may not be generalized to the overall population in Israel, though the amount of “unknown” in our study was relatively small compared to studies from Netherlands [7], Japan and Israel [10,11]. Our study may have encountered bias since some enrolled patients were hospitalized for investigation of FUO after previously undergoing diagnostic tests in the community setting. Another limitation is the lack of data from another rural hospital in our current study which would have improved the comparisons with our previous similar study. We should also bear in mind that the two studies have similar population, but not the same one.

### Conclusion

Infections, mainly bacterial, are still the main cause for FUO in southwest Israel. There is a significant decrease in infectious causes and an increase in autoimmune and malignant causes. “Undiagnosed cases” still compromise a significant group, although declining in size, at least in our study. Most undiagnosed patients have self-limited disease that a later interview revealed. Anemia and elevated level of CRP and ESR is very common among FUO patients. Abdominal CT, blood cultures and biopsies are the most commonly performed, most valuable and most cost beneficial diagnostic tests for FUO diagnosis. The mortality of FUO during hospitalization was found to be low. Most undiagnosed FUO cases will either resolve within days of discharge from the hospital or will be diagnosed in the same or another hospital during the upcoming admission.

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