



Fever of unknown origin: Most frequent causes in adults patients

Febrilno stanje nejasne etiologije: najčešći uzroci kod odraslih bolesnika

Biljana Popovska-Jovičić, Predrag Čanović, Olgica Gajović, Ivana Raković,
Željko Mijailović

Clinic of Infectious Disease, Clinical Center of Kragujevac, Kragujevac, Serbia

Abstract

Background/Aim. The differential diagnosis of fever of unknown origin (FUO) includes more than 200 different diseases and conditions. The aim of this study was to identify the most frequent causes of FUO among adult patients according to gender and age. **Methods.** The study included 74 patients examined from June 2010 to June 2013 at the Infectious Disease Clinic, Clinical Center Kragujevac in Serbia, according to the defined criteria for FUO. The patients were divided according to the diagnosis into four groups: infectious, malignant, rheumatic and “other diseases”. A cause of febricity could not be established in a portion of subjects, and they comprised the group of undiagnosed cases. **Results.** Infectious diseases were dominant in the study, followed by rheumatic diseases, which were most frequently found in women and the elderly. The diseases recognised as the most common causes of febricity were subacute thyroiditis, subacute endocarditis, Still’s disease, rheumatic polymyalgia with or without temporal arteritis, and cytomegalovirus infection. In 44% of the patients, the final diagnosis was composed of only six clinical entities. **Conclusion.** The importance of establishing the diagnosis of rheumatic disease is especially emphasised, in line with other authors’ research indicating the number of these diseases is on the rise. The diagnostic approach to FUO should always be directed to the known frequency of diseases.

Key words:

fever of unknown origin; diagnosis; diagnosis, differential; age groups; sex.

Apstrakt

Uvod/Cilj. Diferencijalna dijagnoza febrilnih stanja nepoznatog porekla (*fever of unknown origin* – FUO), obuhvata preko 200 različitih bolesti i stanja. Cilj rada bio je da se odrede najčešći uzroci FUO prema polu i životnom dobu. **Metode.** Ispitivanjem su obuhvaćena 74 bolesnika koja su u periodu od juna 2010. do juna 2013. godine bila lečena u Infektivnoj klinici Kliničkog centra u Kragujevcu prema definisanim kriterijumima za FUO. Prema dijagnozi bolesnici su svrstani u četiri grupe: infektivne, maligne, reumatske i “druge bolesti”. Kod dela bolesnika nije utvrđen uzrok febrilnosti i oni su činili grupu sa nedijagnostikovanim bolestima. **Rezultati.** U našem istraživanju dominirale su infektivne bolesti, zatim reumatske, najviše zastupljene kod ženskog pola i starije populacije. Bolesti koje su se izdvojile kao najčešći uzroci febrilnosti bile su subakutni tireoiditis, subakutni endokarditis, Stilova bolest, reumatska polimijalgija sa ili bez temporalnog arteritisa i citomegalovirusna infekcija. Kod 44% febrilnih bolesnika završnu dijagnozu činilo je svega šest kliničkih entiteta. **Zaključak.** Posebno se ističe značaj utvrđivanja dijagnoze reumatskih bolesti, čiji je broj u porastu, što je u skladu sa istraživanjima drugih autora. Dijagnostički pristup FUO treba uvek da bude usmeren prema poznatoj frekvenciji bolesti.

Ključne reči:

febrilnost nejasne etiologije; dijagnoza; dijagnoza, diferencijalna; životno doba, grupe; pol.

Introduction

According to the traditionally accepted definition by Petersdorf and Beeson¹ in 1961, fever of unknown origin (FUO) means a repeated occurrence of fever above 38.3°C in the course of three weeks, the origin of which remains unresolved after three visits to the outpatient doctor or seven days of hospital examination. Thirty years later, with the development of modern diagnostic methods, Durack and Street² suggested two significant modifications to the initial definition: differen-

tiation between standard FUO and three other forms of febricity accompanied by neutropenia, nosocomial infections, and human immunodeficiency virus (HIV), and a shorter duration of hospital examinations - three days instead of seven.

FUO represents a great challenge to clinicians because its differential diagnosis is composed of more disorders than in any other medical condition, encompassing both very rare and relatively common entities, classifiable into four groups: infectious, malignant, rheumatic and “other” diseases³⁻⁵. The published papers indicate that the differential diagnosis of fever

includes more than 200 diseases and conditions, none of which with an incidence higher than 5%⁶. A significant portion of patients who remain undiagnosed in spite of the rapid development in diagnostic possibilities cannot be neglected, and recently published studies suggest their number is increasing⁷.

Many researchers have investigated causes of fever in the elderly compared to the young adult population, and their results suggest that the etiologic factors differ in these populations⁸.

The aim of this research was to determine the most common causes of FUO in patients treated at the Infectious Diseases Clinic of the Clinical Center Kragujevac, Serbia, to determine the distribution of various causes of FUO by gender, and to determine the most common causes of FUO in patients younger and older than 65 years.

Methods

The study included 74 adult hospitalized patients examined at the Infectious Diseases Clinic in Clinical Center Kragujevac. All the procedures were approved by the Ethical Committee of the Clinical Center in Kragujevac. Data were retrospectively collected from the medical records in a three-years period, from June 2010 to June 2013. Only the patients with standard FUO, body temperature higher than 38.3°C on several occasions during a three-week period and the origin of fever remaining unknown during three visits to the doctor, or after three days of hospital stay, were included. Patients with neutropenia, nosocomial infections and FUO during HIV infection were excluded from the study. First, all the patients were classified into infectious and non-infectious disease groups. We then divided the patients into the four groups according to the causative disease: infectious, malignancies, rheumatic, and group of "other" diseases not belonging to any of the previously mentioned clinical entities. This group included granulomatous diseases, subacute thyroiditis, inflammatory diseases of the digestive tract as well as drug-induced fever, factitious fever, and habitual hyperthermia. The patients in whom the cause of febricity remained unknown were classified into the group of undiagnosed FUO cases. Classification was then analyzed in relation to patient gender and age. The age limit between the younger and older population was set to 65 years.

The observed data are presented in tabular and graphical form. The results obtained were analysed using the methods of descriptive statistics.

Results

In 28 (37.8%) patients of the 74 examined a disease of infectious origin was diagnosed, while in 43 (58.1%) patients a non-infectious cause of fever was found. In three (4.1%) patients, the cause was not found (Table 1).

Visualizine procedures commonly used for the diagnosis of FUO are shown in Table 2.

In Table 1 it is shown that the majority of patients, 28 (37.8%), had infectious disease followed by 19 patients (25.6%) with rheumatic disease, 13 patients (17.5%) had "other disease", and, finally, 11 patients (14.8%) had malignant disease. The group V was composed of three (4.1%) patients with undiagnosed diseases.

Table 1
Causes of fever of unknown origin (FUO) in total of 74 adults patients

FUO patients' diagnoses	Patients number
Infectious diseases	28 (37.8%)
Cytomegalovirus infection	5
HIV infection	2
Epstein-Barr virus infection	1
staphylococcal sepsis	1
leptospirosis	1
brucellosis	1
ITU	1
Localised Infections	
subacute endocarditis	8
acute cholecystitis	2
tubo-ovarian abscess	1
perinephric abscess	1
pyonephrosis	1
diverticulitis	1
iliopsoas abscesses	1
pulmonary abscess	1
Rheumatic diseases	19 (25.6%)
Still's disease in adults	6
systemic lupus erythematosus	3
<i>Polymyalgia rheumatica</i>	4
temporal arteritis	3
Reiter's syndrome	3
Malignant diseases	11 (14.8%)
colonic neoplasm	3
breast cancer with pleural metastases	1
renal cancer with hepatic and pulmonary metastases	1
lung cancer with thoracic spine metastases	1
prostatic neoplasm	2
pancreatic neoplasm	1
hematologic diseases	
acute myeloid leukaemia	1
Hodgkin's disease	1
Other diseases	13 (17.5%)
subacute thyroiditis	7
Crohn's disease	1
Löfgren syndrome	2
granulomatous hepatitis	1
artificially induced fever	1
drug-induced fever	1
Unknown cause of FUO	3 (4.1%)

Table 2
Visualizing procedures commonly used for the diagnosis of fever of unknown origin

Diagnostic Imaging	Number
Chest X-ray	65
Abdominal ultrasonography	68
Abdominal computed tomography (CT)	27
Thorax computed tomography (CT)	16
Nuclear magnetic resonance (NMR)	7
Positron emission tomography (PET)	2

The diseases recognised as the most common causes of fever were subacute thyroiditis, subacute endocarditis, Still's disease, *polymyalgia rheumatica* and temporal arteritis, and cytomegalovirus infection. The listed diseases were diagnosed in as many as 33 (44%) of the total number of patients

diagnosed with FUO, while the most frequent diagnoses were subacute thyroiditis and subacute endocarditis, together are found to be the cause in every fifth patient with FUO.

Three patients (4.1%) entered the group of unknown causes of FUO. Following discharge from the Infectious Diseases Clinic, an undiagnosed patient experienced spontaneous subsiding of febricity, while maintaining good general condition during the follow-up on the outpatient basis. Autopsy of the second patient revealed malignancy, namely, pancreatic cancer. In the third male patient, three months of febricity accompanied by biohumoral inflammatory syndrome were followed by respiratory failure and death. The diagnosis remained unknown despite exhaustive investigations.

The aim of the study was also to determine gender-wise distribution of different FUO factors. The study included 36 (48.65 %) male and 38 (51.35 %) female patients. The obtained results suggested that in the female population, the most common were rheumatic diseases, 12 (31.5%). They are followed by infections in 11 (28.9%) of the patients, "other diseases" in 8 (21.1%), and malignant diseases in 7 (18.4%) of the patients (Figure 1). All FUO cases in the female patients were diagnosed. Most of the male patients, 17 (47.2%), had infectious disease, followed by significantly lower percentages of rheumatic, 7 (19.4%), "other diseases", 5 (13.8%), and malignancies, 4 (11.1%). Three (8.3%) of the patients entered the group of unknown FUO factors (Figure 1).

Among the patients in our study 48 (64.8%) were under 65 years of age (Figure 2). The most common diagnosis was that of infectious disease, in 21 (43.7%) patients. Viral diseases dominated among them, and were found in eight patients. Cytomegalovirus infection had the highest incidence, verified by serological methods (ELISA test) in five patients. The second most common diagnosis was rheumatic diseases, found in 10 patients (20.8%), especially Still's disease, followed by systemic *lupus erythematosus*. Malignant diseases comprised a significant percentage of conditions in the population under 65, occurring in nine (18.7%) patients. Hematologic diseases were only found within this population, namely acute myeloid leukemia and Hodgkin's disease. Both patients were under 40 years of age.

In the age group over 65 years, comprising 26 (35.1%) patients, the largest number of patients belonged to the group with rheumatic conditions, nine (34.6%) patients. The group was dominated by *polymyalgia rheumatica* and temporal arteritis as separate clinical entities. The group with infectious diseases was the second largest (Figure 2). Localised infections, especially subacute endocarditis, were verified in seven patients in this group. Subacute thyroiditis dominated the "other diseases" group, diagnosed using the radioactive iodine fixation test. Malignancies were confirmed using diagnostic imaging and histopathologic findings in 2 (7.6%) of the patients.

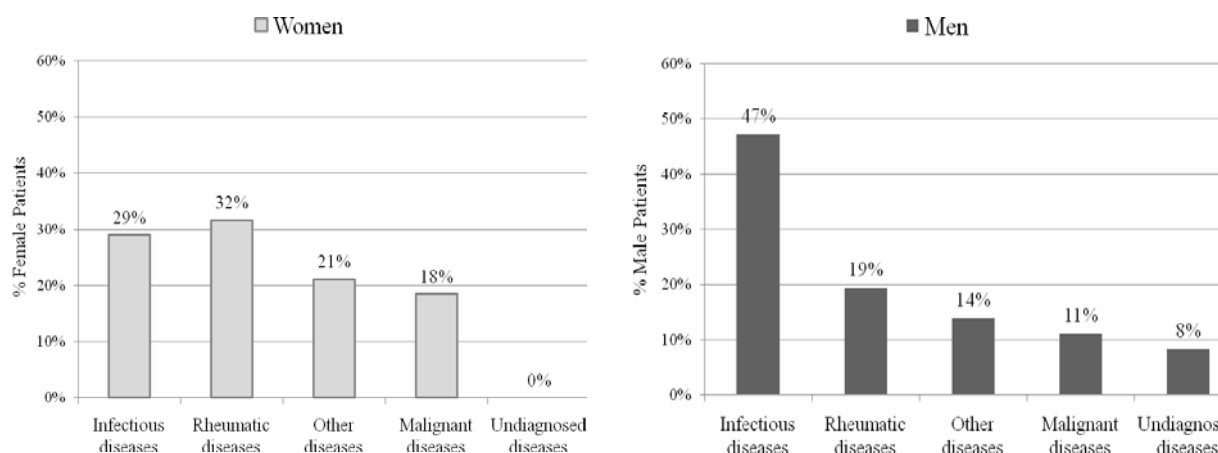


Fig. 1 – Most common etiologies of fever of unknown origin according to gender.

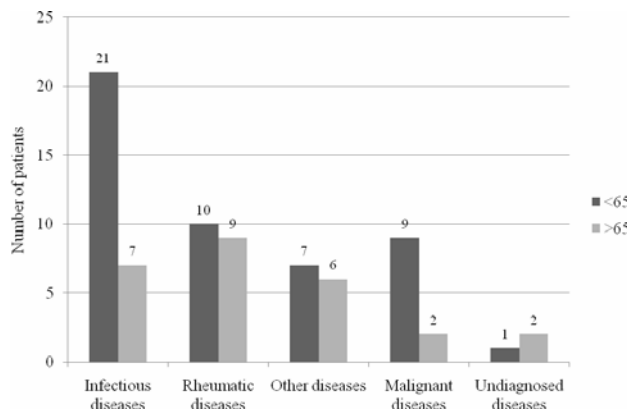


Fig. 2 – Most common etiologies of fever of unknown origin (FUO) according to age
 ■ – patient with FUO under 65 years old; ■ – patients with FUO above 65 years old.

Discussion

The share of etiologies in the diagnosis of FUO has continuously changed since 1960. In the past two decades, certain authors have suggested a decreased incidence of infectious and malignant diseases, with the increase in the frequency of rheumatic diseases^{9,10}. A recent research continues to pinpoint infections as the leading causes of FUO, which is consistent with our results. In a group of non-infectious FUO, the causes according to other authors¹¹ are, malignancies, as the most numerous, followed by rheumatic diseases. However, our research indicates that the leading FUO causes among the non-infectious diseases were rheumatic conditions, while malignancies appeared as low as the fourth place.

The development of modern diagnostic procedures continuously modifies the spectrum of diseases with FUO. Introduction of diagnostic imaging, such as echosonography, computed tomography and magnetic resonance imaging, has contributed to the rapid diagnosis of solid tumours and abscesses, which in turn influenced the number of infectious and malignant diseases in our FUO sample¹². Table 2 shows visualizing procedures commonly used in the diagnostic of FUO patients. The invention and widespread use of serological analysis enabled faster detection of many viral diseases, which reduced their frequency within FUO¹¹. Besides serology, in the diagnostic of other infections and infectious diseases we used microbiology tests, as well as polymerase chain reaction.

In our research, subacute endocarditis was the most common disease in the infectious diseases group and was especially dominant in the elderly population. Subacute endocarditis was present in 28% of patients with infectious diseases, a significant percentage given the available diagnostic procedures such as echocardiography. Diagnose determination was based on characteristic clinical findings and findings of vegetations on the heart valves. Using hemoculture *Streptococcus viridans* was isolated in three patients, *Staphylococcus aureus* in one, while in other patients no etiologic agent was isolated. It is believed that changes in the heart valves as well as the increased likelihood of sepsis make the elderly population more vulnerable to the development of endocarditis¹³.

The obtained results indicate that cytomegalovirus infection is the most common etiologic cause of viral disease. Clinical diagnosis of cytomegalovirus infection can be difficult due to a high prevalence of asymptomatic infections and various clinical presentations of the disease. Increased activity of liver enzymes and splenomegaly, were the main parameters which directed us towards the diagnosis of cytomegalovirus infection. Seroprevalence, ranging from 50% to 80% before

40 years of age, also represents a significant cause of FUO in the middle-aged population.

Among the subjects in the "other diseases" group, subacute thyroiditis was undeniably the most common one. This endocrinologic condition was also dominant among female subjects in our sample. Subacute thyroiditis is a known cause of FUO, although the diagnosis may prove more difficult to make in the absence of typical symptoms, such as frontal neck pain¹⁴.

Some authors set hematological diseases and colorectal cancer apart as the common causes of FUO in the group with malignancies¹⁰. These diseases were also verified in our sample, especially in the young adult population. Apart from those conditions mentioned above, no other malignancies causing febricitis were detected.

According to many authors, the diagnosis of FUO differs between older and younger populations⁸, a presumption also confirmed by our study. In the elderly population, the most numerous are rheumatic conditions, while the younger population is dominated by infections, especially viral ones. *Polymyalgia rheumatica* and temporal arteritis, both as joint and separate clinical entities, are most commonly found in the elderly, which is a conclusion drawn by many other authors¹⁵. For these diseases to appear among the common causes, contributing factors are certainly the subacute course of disease and non-specific symptoms.

In the group of rheumatic patients under the age of 60, Still's disease is the most frequent clinical entity. This multisystem disease can affect joints, skin, eyes, liver and spleen, but not all patients exhibit all symptoms¹⁶. A review of the available literature revealed that many authors emphasise Still's disease as an important cause of FUO which is the fact that should be given particular consideration because the criteria for the diagnosis require the exclusion of other rheumatic, malignant and infectious diseases¹⁷.

Due to lack of specific tests in the diagnostics of Still's disease and rheumatic polymyalgia, the diagnosis was established using immunological, serological and microbiological analysis by which we excluded other diseases¹⁸.

Conclusion

Our study shows that only six causes account for 44% of final diagnoses. The influence of rheumatic diseases is especially emphasised, particularly in elderly persons, in line with other authors' research indicating that the number of these diseases is on the rise. A diagnostic approach to fever of unknown disease should always be directed to the known frequency of causing diseases. The first step is to rule out the common causes of fever of unknown disease and then review the less known causes.

R E F E R E N C E S

1. *Petersdorf RG, Beeson PB.* Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore)* 1961; 40: 1–30.
2. *Durack DT, Street AC.* Fever of unknown origin--reexamined and redefined. *Curr Clin Top Infect Dis* 1991; 11: 35–51.
3. *Knockaert DC, Vanderschueren S, Blockmans D.* Fever of unknown origin in adults: 40 years on. *J Intern Med* 2003; 253(3): 263–75.
4. *Cunha BA.* Fever of unknown origin: focused diagnostic approach based on clinical clues from the history, physical examination, and laboratory tests. *Infect Dis Clin North Am* 2007; 21(4): 1137–87.
5. *Ergönül O, Wilke A, Azap A, Tekeli E.* Revised definition of 'fever of unknown origin': limitations and opportunities. *J Infect* 2005; 50(1): 1–5.
6. *Finch RG, Davies GR, Čivljak R.* Fever of unknown origin. In: *Begovac J, Božnović D, Lisić M*, editors. *Infectology*. 1st ed. Zagreb: Profil International; 2006. p. 123–7. (Croatian)
7. *Horowitz HW.* Fever of unknown origin or fever of too many origins. *N Engl J Med* 2013; 368(3): 197–9.
8. *Gleckman RA, Esposito AL.* Fever of unknown origin in older patients. *Geriatrics* 1984; 39: 46–51.
9. *Gaeta GB, Fusco FM, Nardiello S.* Fever of unknown origin: a systematic review of the literature for 1995-2004. *Nucl Med Commun* 2006; 27(3): 205–11.
10. *Zenone T.* Fever of unknown origin in adults: evaluation of 144 cases in a non-university hospital. *Scand J Infect Dis* 2006; 38(8): 632–8.
11. *Chan-Tack KM, Cunha BA, Bartlett J, Sanders CV, Talavera F.* Fever unknown origin. *Medscape from WebMD* 2011 [serial on the Internet]. Available from: <http://emedicine.medscape.com/article/217675-overview> [cited 2012 July 8].
12. *Bleeker-Rovers CP, Vos FJ, de Kleijn EM, Mudde AH, Dofferhoff TS, Richter C*, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. *Medicine (Baltimore)* 2007; 86(1): 26–38.
13. *Turkculov V, Brkić S, Sević S, Marić D, Tomić S.* Fever of unknown origin in elderly patients. *Srp Arh Celok Lek* 2011; 139(1–2): 64–8.
14. *Cunha BA, Thermidor M, Mohan S, Valsamis AS, Johnson DH, Brook M*, et al. Fever of unknown origin: Subacute thyroiditis versus typhoid fever. *Heart Lung* 2005; 33(6): 417–21.
15. *Tal S, Guller V, Gurevich A, Levi S.* Fever of unknown origin in the elderly. *J Intern Med* 2002; 252(4): 295–304.
16. *Uppal SS, Al-Mutairi M, Hayat S, Abraham M, Malaviya A.* Ten years of clinical experience with adult onset Still's disease: is the outcome improving. *Clin Rheumatol* 2007; 26(7): 1055–60.
17. *Kucukardali Y, Oncul O, Camuslu S, Danaci M, Calangu S, Erdem H*, et al. The spectrum of diseases causing fever of unknown origin in Turkey: a multicenter study. *Int J Infect Dis* 2008; 12(1): 71–9.
18. *Cunha BA.* Fever of unknown origin caused by adult juvenile rheumatoid arthritis: the diagnostic significance of double quotidian fevers and elevated serum ferritin levels. *Heart Lung* 2004; 33(6): 417–21.

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