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INVITED REVIEW – OPEN ACCESS

Fever of Unknown Origin (FUO): Towards a Uniform Definition and Classification System

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ABSTRACT

Despite the great advancements seen in medicine in recent years, fever of unknown origin (FUO) remains a serious diagnostic challenge. Regardless of the etiological elucidation in many cases of FUO and the progress seen in the management of these patients, there are currently many weaknesses in this area as a result of inconsistency in the definition and interpretation of key terminology and the utilization of different definitions and classifications. As a result, there is confusion among medical practitioners about FUO, which leads to laborious and difficult comparisons among different case series. This study outlines the mismatch in terminology and diversity found in the classification of the conditions that cause FUO and emphasizes the discrepancies between what some terminology intends to represent and what it actually represents in reality. Thus, we attempted to determine an appropriate solution for established inconsistencies.

Keywords: Diagnostic approach, fever, fever of unknown origin, infection, neoplasm

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INTRODUCTION

Fever is a common clinical manifestation in humans throughout their existence, and for a long time, it was considered a disease. This notion changed in the late 18th century after Fahrenheit constructed the first effective thermometer, and later in the 19th century, Carl Wunderlich implemented the concept of clinical temperature charts. With these findings, it became obvious that fever does not represent a disease but rather is an accompanying sign of a disease (1). Sir William Osler (who lived from 1849–1919) noted "fever was by far the greatest, and the most terrible humanity enemies, together with famine and wars" (2). He lived in the 19th century, when febrile illness caused more than two-thirds of all deaths (2).

Normal body temperature is a dynamic parameter with physiological oscillations and considerable individual variability. Temperature can vary depending on age, sex, physiological activity, menstrual cycle phases, food intake, circadian oscillations, anatomic site of measurement, and environmental temperature. A normal oral temperature in 99% of the population ranges from 36.0°C to 37.7°C, with a circadian variation of 1°C or greater between the morning nadir and the evening peak. The mean oral temperature is 36.8±0.4°C, and it is slightly higher in women than in men (36.9° vs. 36.7°C) (3).

One of the most challenging clinical syndromes related to elevated body temperature is fever of unknown origin (FUO). Despite the immense expansion of medical sciences, FUO currently remains a complex clinical entity and serious diagnostic challenge (4). The true incidence and prevalence of FUO are unknown. FUO accounts for approximately 3% of hospital admissions and has a high impact on health care systems (5). According to a study from a university hospital in Japan, FUO occurred in 153 of 5.245 (2.9%) hospitalized patients (6). In another study from a community hospital in the USA, 1 of every 73 infectious disease consultations was due to FUO (7).

In recent decades, there have been numerous published manuscripts that focus on the causes of and diagnostic protocols for FUO or the best treatment approach and prognosis in patients with FUO. Although there are variations depending on the geographic distribution and some social and economic factors, the authors unanimously agree that the majority of cases of FUO result from unawareness of atypical manifestations of common diseases and are rarely due to exotic diseases (8). In addition, the lack of detailed bedside evaluation, delays in advising specific investigations, misinterpretation of clinical features and investigation results, false negative tests, and multiple pathologies in the same patient are some potential factors that influence FUO appearance (2).

In a clinical and academic study on FUO, profound nonuniformity and diversity of the definitions and classifications used were found. This global inconsistency in the definition and interpretation of the clinical terminology as well as the difference in the definitions and categories used in FUO cause confusion and further impede or disable comparisons among different case series. The absence of uniformity can mainly be observed in the defini-

tions used for fever and FUO itself; content of the initial diagnostic protocol; terminology and classification of diagnostic categories; distribution of particular diseases as etiological causes of FUO in appropriate diagnostic categories; and how much the term FUO is compatible with the factual circumstances in which it is used and its differentiation from other similar terms.

Our aim was to discuss the above-mentioned irregularities concerning FUO and to attempt to determine an appropriate solution for their unification.

Definition of Fever

In body temperature measurements, the cut-off value between normal body temperature and fever remains disputed. One of the most accepted definitions for fever is a morning temperature ≥37.2°C or a temperature ≥37.8°C at any time during the day when taken orally or >38.3°C when measured rectally (2, 9). Similarly, an accepted definition for fever is the endogenous elevation of at least one measured body temperature to ≥38°C, regardless of the level of activity, meals, time of day, anatomic site of measurement, type of thermometer, age, or environmental conditions during the measurement (10). In clinical settings, there are many other definitions for fever. Unfortunately, the timing, anatomic site, and method of temperature monitoring is not mentioned in most FUO studies (11). However, there are concessions from the adopted definitions for normal body temperature for fever, such as >38.0°C taken rectally (12, 13), >37.5°C (14) or >38.1°C (15) taken orally, or ≥37.0°C (16), ≥37.5°C (17, 18), ≥37.8°C (19), or ≥38.0°C (20) measured in the axillae, in some studies.

Definition of FUO

FUO (or pyrexia of undetermined, undefined, unexplained, or uncertain origin) describes a syndrome of fever that does not spontaneously resolve in the period expected for self-limited infections and in which the cause remains elusive after a considerable diagnostic workup (11, 21, 22). FUO definitions are remarkably variable and somewhat arbitrary and variable over time.

The first reliable definition for FUO was developed by Petersdorf and Beesn in 1961. They defined FUO as [1] a temperature >38.3°C on several occasions [2] with a duration of more than three weeks and [3] failure to reach a diagnosis despite one week of inpatient investigations (23). The purpose of these criteria was to exclude acute, self-limited, frequently viral diseases, healthy people whose temperatures slightly exceed the normal range (i.e., those with habitual hyperthermia), and disorders readily identifiable after a brief evaluation after enough time is allowed to complete initial investigations (8, 24, 25).

Since this first definition was published, several attempts for its modification have been proposed, considering that a hospital stay of one week is a time defined by conditional criteria and can produce different results from investigations, which mainly depend on physician experience, equipment, and differences in the diagnostic workup among different hospitals (26). In 1991, the definition of FUO was updated by Durack and Street (27). They replaced the last criterion with "uncertain diagnosis after 3 days of hospital stay or more than 2 outpatient visits" to respond to the evolving trends in clinical practice (second FUO definition). In addition, these authors proposed four groups (subsets) of FUO: classic, nosocomial (healthcare-associated), HIV-related, and neutropenic (immunodeficient). Among these subsets, only classic FUO is included in our discussion. Three days are required for classical cultures or skin tests and the necessary imaging to be adequately interpreted (28). The proposed time period in this definition is quantitative, rather than arbitrary, and it does not represent an improvement, as more than three days are frequently necessary to obtain the results from classical cultures and serology tests (26). The option for outpatient investigation was offered, since illness severity does not necessitate hospitalization in the majority of these patients and expenditures associated with inpatient treatment can be decreased with outpatient care. It is also disputed whether "3 days of hospital stay" is analogous to "more than 2 outpatient visits" (8).

In addition to the improvement in diagnostic methods, it became obvious that the type of diagnostic panel is more important than the duration of investigations and that it would be better if in the definition of FUO, a quantitative time defined criterion was replaced with a qualitative baseline set of obligatory investigations, which would include biochemistry, blood and urine cultures, basic imaging procedures, and a set of infectious disease screening tests determined from local epidemiological data (third FUO definition) (5, 26, 29–31). In short, this attempt at a reformed definition proposed to change the quantitative criterion of the time period during which no diagnosis is made to a qualitative one via an initial appropriate intelligent standard diagnostic inpatient or outpatient workup. The purpose of these obligatory diagnostic investigations is to minimize diversity in diagnostic management caused by individual experience of the physicians and by the differences in diagnostic facilities among hospitals and countries (28) and to enable easier and adequate comparisons among different case series with FUO (31).

In the newest modifications of this third FUO definition, two additions are mentioned: the temperature is allowed to be lower than 38.3°C if laboratory signs of inflammation (e.g., elevated erythrocyte sedimentation rate [ESR] and/or C-reactive protein [CRP] levels) are present on several occasions (28, 32); and nosocomial fever and fever in severely immunocompromised patients (WBC <1.0x109/L, neutrophils 0.5x109/L, IgG <50%, use of ≥10 mg prednisone for at least 2 weeks) are excluded (29, 30).

To use the definition of FUO, not only were modifications in the height of the fever and anatomic places of measurement made (as previously shown) but also attempts of some authors were made to shorten its duration from three to two weeks (14, 33).

The current absence of a consensus on which definition for FUO is the most adequate permits many studies to use the definitions from 1961 (34–38) and 1991 (12, 34, 39, 40), which makes comparisons among different studies challenging. For example, one study included 979 patients with FUO according to the definition from 1991, and only 555 of them met the criteria for FUO according to the definition from 1961 (41). In another study, only 59 patients out of 80 with FUO according to the definition from 1991 fulfilled the criteria for FUO according to the 1961 definition (34). Not only the number of patients but also the frequency of diagnostic categories can differ if various definitions for FUO are used. According to Vanderschueren et al., 43.9% of cases were in the category undiagnosed if the definition from 1991 was used, and

53.0% were undiagnosed according to 1961 definition; however, no significant differences in diagnostic categories among diagnosed cases were noted (8). In a systematic review, the frequency of FUO from neoplasms was lower in patients selected with the definition from 1991, and the frequency of FUO from non-infectious inflammatory disorders (NIIDs) was lower in patients with the third FUO definition (31). Infections were more prominent, although not significantly, when the definition from 1991 was used compared to when the definition from 1961 was used (34).

Uniform Initial Diagnostic Protocol

Defining the necessary initial investigations to try to reach a diagnosis remains a matter of debate, but it is generally agreed that the standard initial diagnostic investigation protocol should at least include a comprehensive history and repeated physical examination, complete blood count with differential cell count, electrolytes, renal and liver function tests, protein electrophoresis, enzymes (alkaline phosphatase, aminotransferase, lactate dehydrogenase, creatine phosphokinase), CRP, ESR, microscopic urinalysis, three blood cultures (different sites, several hours apart), urine culture, chest X-ray, abdominal ultrasonography, a tuberculin skin test or interferon gamma release assay, which is quite often accompanied by testing for antinuclear antibodies, rheumatoid factor, and anti-HIV test (26, 29–31, 42–44). Further evaluations indicated by potentially diagnostic clues, which are defined as all localizing signs, symptoms, laboratory tests, and other abnormalities potentially pointing towards a diagnosis, can additionally be included (5, 21, 28, 30, 42).

Literature reviews acknowledge that the initial diagnostic protocol in many of the studies was enriched with additional analyses, such as ferritin (45), angiotensin converting enzyme (5, 21), antistreptolysin-O test (35), sinus radiography (35), chest and abdominal CT-scan (5, 21, 28, 33, 44–46), and serological diagnostic tests in accordance with the regional epidemiological situation (8, 28), such as Widal and Wright agglutination test (35), Cytomegalovirus-IgM and Epstein Barr virus serology (21, 28, 33, 44), and hepatitis and Toxoplasma serology (33).

Classification of Diagnostic Categories and Their Distribution

Different authors show some variability in creating diagnostic categories and nomenclature. Infectious diseases, malignant (neoplastic, oncological, tumors) diseases, miscellaneous (other) disorders and the group of patients who remain without an etiological explanation for fever (undiagnosed) have been attempted to be classified. The main difference is in the group that in recent attempts for classification was designated as NIIDs and encompasses connective tissue diseases (systemic rheumatic diseases), vasculitic syndromes, and granulomatous disorders (8, 26, 39), and in the most recent studies, auto-inflammatory syndromes (29, 42, 45).

As an alternative for the group of NIIDs, different authors use other terminology and classifications, such as rheumatologic (24), inflammatory (43), rheumatologic/inflammatory (5, 47), autoimmune (36), allergic and autoimmune (48), connective tissue (2, 49), inflammatory/connective tissue (50), or collagen vascular (6, 12, 37) disorders. In older studies, other classifications can be found in which in addition to the standard diagnostic categories (infections, neoplasms, miscellaneous, undiagnosed), the following are independent categories: inflammatory, collagen vascular and granulomatous diseases (7), collagen and granulomatous diseases (51), collagen, granulomatous diseases, periodic fever and factitious fever (52), multisystem diseases, drug fever, factitious fever and habitual hyperthermia (22), etc. As an illustration of such diversity, granulomatous diseases are in the NIIDs category according to some authors (26, 39, 53) and in the miscellaneous category according to others (6, 24, 37) or can even form their own category (7, 51, 52).

The proportion of diagnostic categories reserved for patients with FUO varies widely in global literature. Therefore, the frequency of infections, NIIDs, and neoplasms are observed in ranges from 11% to 59%, 2% to 38%, and 6% to 31%, respectively (17). The frequency of miscellaneous conditions and undiagnosed cases was reported to be 2% to 22% and 5% to 53%, respectively (17). The reasons for these discrepancies could be due to a plethora of factors, such as different inclusion criteria (which depend on the FUO definition); the time period in which the study was conducted (in the latest period there was an increasing number of drug addicts, immigration, international travel, people with various prosthetic implants, development of new diagnostic techniques, revelation of new infective causes that might present with fever of unknown origin such as ehrlichiosis, Bartonellosis, persistent Yersinia infection, and Parvo B19, HTLV-1, and HHV8 viruses) (28, 54); the nature of the study (prospective or retrospective); the demographic characteristics of the included population; and the geographic region and its economic characteristics (including the hospital in which the study was conducted with its diagnostic potential and physician experience).

Distribution of Different Diseases in Appropriate Categories

Although highly desirable, the development of a uniform classification system is far from obtainable at present, which is mostly due to the lack of a uniform disease classification inside the diagnostic categories among other factors.

Whipple's disease is usually part of the miscellaneous group but increasingly more frequently is part of the infection category (28, 36, 47, 55). In different reports, Castleman's disease is included in the neoplastic group (20, 56), miscellaneous group (6, 29, 42, 57, 58), or infectious diseases group (47, 55), and atrial myxoma sometimes is classified in the miscellaneous group (28, 42, 51, 52) and other times is classified in the neoplastic group (5, 11, 36, 43, 55). In some reports, Kikuchi disease (2, 9, 29, 50, 54, 57) and Crohn's disease are classified as part of the miscellaneous group (6, 21, 37, 55–57, 59), and in other reports, Kikuchi disease (5, 49) and Crohn's disease (11, 33, 39) are in the NIIDs group. Discussions can further expand to whether subacute thyroiditis, autoimmune hepatitis, and primary sclerosing cholangitis from the miscellaneous group can be transferred to the NIIDs group (8, 60) and if Crohn's disease (52) and Hashimoto thyroiditis (48) should be considered granulomatous diseases.

An excellent example of this discord in the classification and terminology is Familial Mediterranean Fever (FMF), which according to one classification is in the miscellaneous group (24, 37, 42, 47, 49, 52, 55, 56) and according to others is in the NIIDs group (5, 12, 29, 43, 45). Furthermore, FMF is declared to be inherited (12, 24,

36), a hereditary autoinflammatory disorder (29, 45, 55, 58), or it can be part of familial periodic fever syndromes (47), while Knockaert categorizes this disease in the group of familial autoinflammatory syndromes and hereditary periodic fever syndromes (25).

Although various authors classify granulomatous hepatitis as a part of the defined diagnostic categories (37, 51, 52, 54), others simply consider this condition a histologic reaction caused by numerous well-defined conditions that should be additionally diagnosed; according to them, cases of granulomatous hepatitis are part of the undiagnosed category (25, 53). Several other clinical entities, such as erythema nodosum (51), nonspecific pericarditis (51, 52), idiopathic granulomatosis (59), or unclassified connective tissue disorders (6), which are accepted as a cause of FUO by some authors but are not recognized as a diagnostically clear cause of FUO by others and are placed in the undiagnosed group.

Thus, we can partially explain the high percentage of undiagnosed cases of FUO reported from specialized centers in developed countries that is paradoxically higher than the ones reported from secondary care hospitals in developed countries and tertiary care hospitals in the developing world. Another reason for this occurrence is that these specialized centers often are referred many filtered patients (i.e., patients who were already examined in other hospitals and have undergone many examinations without a successful diagnosis).

The Term FUO and its Adequacy

There are a few terms in the literature that are similar but not identical to FUO. Accordingly, the term prolonged unexplained fever (PUF) has been defined as a more extensive term than FUO, since it should include the first two criteria for FUO with the possibility to become FUO after conveying an initial qualitative diagnostic protocol (8), although the terminological analysis of these two terms cannot make this conclusion. Interestingly, the term PUF in pediatrics was defined by Statler and Marshal as a fever that lasts for a longer period of time than expected for a typical illness duration, and compared to FUO, seems to be more adequate, as the term FUO does not convey the fact that the problem is the length of time the fever has persisted (10). According to Statler and Marshall, PUF and recurrent unexplained fever (i.e., fever episodes that occur at frequent intervals) are considered components of undifferentiated fever (i.e., fever as the main symptom without other clinical features that suggest an etiology) (10). Prolonged perplexing fever and fever without an immediately apparent etiology (61), although terminologically more competent, represent an unsuccessful alternative to what FUO should currently represent.

The term inflammation of unknown origin (IUO) is defined as FUO with a temperature that does not exceed 38.3°C but is accompanied by elevated inflammatory markers (i.e., CRP and/or ESR) on several occasions (which corresponds to one of the modifications in the newest FUO definition), and the diagnostic approaches used in FUO are identical to those that should be used in IUO (9). A term compatible with the latest definition is low-grade (prolonged) fever, which is defined as a body temperature continuously or intermittently between 37.5°C and 38.3°C with other criteria applicable to FUO with or without increased inflammatory markers (18, 28). If inflammatory markers are increased, this condition requires the same methodological diagnostic approach as FUO, considering the same etiological spectrum in these two conditions (18). In contrast, if the inflammatory markers are normal, habitual hyperthermia should be considered (18). Finally, the term fever of intermediate duration refers to a fever higher than 38.0°C that lasts 7–28 days and remains undiagnosed (13).

In pediatrics, there are two terms that are identical in terminology to FUO but are designed to designate different clinical conditions: fever without a source and fever without a focus. The term fever without a source should define the occurrence of fever for one week or less in a child with no adequate explanation determined by a medical history or physical examination (62). Fever without a focus is defined as a rectal temperature of 38°C or higher as the sole presenting feature and includes two subcategories: fever without localizing signs, which is defined as a fever of acute onset and duration of <1 week, and FUO (58).

Lastly, there is a dilemma about the adequacy of the term FUO in addition to its universal acceptance and whether it accurately reflects the true condition that should be defined. A literary analysis of the words that define FUO depicts a febrile condition in which there is an undiagnosed condition for a fever. Accordingly, the term FUO does not correspond and is inappropriate for the condition that it should represent for two reasons:

[a] The term FUO by itself does not disclose that the fever should arbitrarily last for at least three weeks. Considering that the term FUO does not define the duration of a fever, it is logical that FUO should represent all febrile conditions, which remain etiologically undiagnosed (regardless of the fact if the cause was sought for or not) independent of their duration. In this context, Bryan suggested the replacement of the term FUO with prolonged FUO (≥3 weeks) (61).

[b] In some patients with prolonged fever, after investigations and follow up are conducted, an etiologic cause is found. Logically, these patients are no longer exclusively categorized in the FUO group; they are categorized as having fever with a known origin. Consequently, the question arises whether the term FUO (according to current understanding) should be used only for the group of patients in which the diagnosis remains elusive even after extensive investigations have been conducted.

This kind of reflection is without pretension or any expectations that could influence a revision in the terminology of this condition, as we are talking about the decades long and widely accepted term FUO, which by itself represents a label and deeply infiltrated term, or brand. We suggest that the initial working diagnosis for patients that fulfill the current criteria for FUO (regardless of the definition used) until their complete etiological identification should be prolonged febrile condition (status febrilis prolongata in Latin), which would eventually evolve to prolonged febrile condition with infection, neoplasm, NIIDs, or miscellaneous condition or with an unknown origin (undiagnosed).

We would like to send an appeal for an initiative performed by the leading world centers for FUO, which would advocate for global uniformity in the definition and classification of patients with prolonged fever through a consensus-based approach. Furthermore, the aspiration for uniformity could eventually expand and influence the diagnostic and therapeutic approaches in these patients.

CONCLUSION

FUO remains a serious diagnostic challenge and is confusing with the ongoing diversity in terminology regarding the definitions used for fever and FUO. Additionally, there is an inconsistency in the selection of the diagnostic categories for FUO and in the allocation of some diseases in a respective diagnostic category. Thus, augmented with the idea that the term FUO itself is not suitable for the conditions that it represents, there is a necessity to construct new global and uniform definitions and classifications of the patients with prolonged fever via a consensus-based approach.

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REFERENCES

1. Welsby PD. Pyrexia of unknown origin sixty years on. Postgrad Med J 1985; 61(720): 887–894. [CrossRef]
2. Ramamoorthy K, Bang M. Pyrexia of unknown origin. API India. Medicine CME 2004. p. 385–90.
3. Leggett JE. Approach to fever or suspected infection in the normal host. In: Goldman L, Schafer AI, editors. Goldman-Cecil Medicine. 25th ed. Philadelphia, PA: Elsevier Saunders; 2016. p.1849–54.
4. Bosilkovski M, Dimzova M, Cvetkova M, Poposki K, Spasovska K, Vidinic I. The changing pattern of fever of unknown origin in the Republic of North Macedonia. Rom J Intern Med 2019; 57(3): 248–53.
5. Cunha BA. Fever of unknown origin: clinical overview of classic and current concepts [published correction appears in Infect Dis Clin North Am. 2008 Jun;22(2):xv]. Infect Dis Clin North Am 2007; 21(4): 867–vii. [CrossRef]
6. Iikuni Y, Okada J, Kondo H, Kashiwazaki S. Current fever of unknown origin 1982-1992. Intern Med 1994; 33(2): 67–73. [CrossRef]
7. Kazanjian PH. Fever of unknown origin: review of 86 patients treated in community hospitals. Clin Infect Dis 1992; 15(6): 968–73. [CrossRef]
8. Vanderschueren S, Knockaert D, Adriaenssens T, Demey W, Durnez A, Blockmans D, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. Arch Intern Med 2003; 163(9): 1033-41.
9. Vanderschueren S, Del Biondo E, Ruttens D, Van Boxelaer I, Wauters E, Knockaert DD. Inflammation of unknown origin versus fever of unknown origin: two of a kind. Eur J Intern Med 2009; 20(4): 415–8.
10. Statler VA, Marshall GS. Evaluation of Prolonged and Recurrent Unexplained Fevers. Pediatr Ann 2018; 47(9): e347–53. [CrossRef]
11. Agarwal PK, Gogia A. Fever of unknown origin. J Assoc Physicians India 2004; 52: 314–8.
12. Mete B, Vanli E, Yemisen M, Balkan II, Dagtekin H, Ozaras R, et al. The role of invasive and non-invasive procedures in diagnosing fever of unknown origin. Int J Med Sci 2012; 9(8): 682–9. [CrossRef]
13. Espinosa N, Cañas E, Bernabeu-Wittel M, Martín A, Viciana P, Pachón J. The changing etiology of fever of intermediate duration. Enferm Infecc Microbiol Clin 2010; 28(7): 416–20. [CrossRef]
14. Whitehead TC, Davidson RN. Pyrexia of unknown origin: changing epidemiology. Curr Opin Infect Dis 1997; 10(2): 134–8. [CrossRef]
15. Vickery DM, Quinnell RK. Fever of unknown origin. An algorithmic approach. JAMA 1977; 238(20): 2183–8. [CrossRef]
16. Goto M, Koyama H, Takahashi O, Fukui T. A retrospective review of 226 hospitalized patients with fever. Intern Med 2007; 46(1): 17–22.
17. Bosilkovski M, Dimzova M, Stevanović M, Cvetkovska VS, Duganovska MV. Fever of unknown origin--diagnostic methods in a European developing country. Vojnosanit Pregl 2016; 73(6): 553–8. [CrossRef]
18. Affronti M, Mansueto P, Soresi M, Abbene AM, Affronti A, Valenti M, et al. Low-grade fever: how to distinguish organic from non-organic forms. Int J Clin Pract 2010; 64(3): 316–21. [CrossRef]
19. Santana LFE, Rodrigues MS, Silva MPA, Brito RJVC, Nicacio JM, Duarte RMSC, et al. Fever of unknown origin - a literature review. Rev Assoc Med Bras (1992) 2019; 65(8): 1109–15. [CrossRef]
20. Naito T, Torikai K, Mizooka M, Mitsumoto F, Kanazawa K, Ohno S, et al. Relationships between Causes of Fever of Unknown Origin and Inflammatory Markers: A Multicenter Collaborative Retrospective Study. Intern Med 2015; 54(16): 1989–94. [CrossRef]
21. Arnow PM, Flaherty JP. Fever of unknown origin. Lancet 1997; 350(9077): 575–80. [CrossRef]
22. Tal S, Guller V, Gurevich A, Levi S. Fever of unknown origin in the elderly. J Intern Med 2002; 252(4): 295–304. [CrossRef]
23. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961; 40: 1–30. [CrossRef]
24. Hirschmann JV. Fever of unknown origin in adults. Clin Infect Dis 1997; 24(3): 291–302. [CrossRef]
25. Knockaert DC. Recurrent fevers of unknown origin. Infect Dis Clin North Am 2007; 21(4): 1189–xi. [CrossRef]
26. de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997; 76(6): 392–400. [CrossRef]
27. Durack DT, Street AC. Fever of unknown origin--reexamined and redefined. Curr Clin Top Infect Dis 1991; 11: 35–51.
28. Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J Intern Med 2003; 253(3): 263–75.
29. Bleeker-Rovers CP, van der Meer JWM, Beeching NJ. Fever. Medicine 2009; 37(1): 28–34. [CrossRef]
30. De Kleijn EMH, Knockaert DC, van der Meer JWM. Fever of unknown origin: a new definition and proposal for diagnostic work-up. European J Internal Medicine 2000; 11(1): 1–3. [CrossRef]
31. Fusco FM, Pisapia R, Nardiello S, Cicala SD, Gaeta GB, Brancaccio G. Fever of unknown origin (FUO): which are the factors influencing the final diagnosis? A 2005-2015 systematic review. BMC Infect Dis 2019; 19(1): 653. [CrossRef]
32. Vanderschueren S, Eyckmans T, De Munter P, Knockaert D. Mortality in patients presenting with fever of unknown origin. Acta Clin Belg 2014; 69(1): 12–6. [CrossRef]
33. Arce-Salinas CA, Morales-Velázquez JL, Villaseñor-Ovies P, Muro-Cruz D. Classical fever of unknown origin (FUO): current causes in Mexico. Rev Invest Clin 2005; 57(6): 762–9.
34. Ergönül O, Willke A, Azap A, Tekeli E. Revised definition of 'fever of unknown origin': limitations and opportunities. J Infect 2005; 50(1): 1–5. [CrossRef]
35. Colpan A, Onguru P, Erbay A, Akinci E, Cevik MA, Eren SS, et al. Fever of unknown origin: analysis of 71 consecutive cases. Am J Med Sci 2007; 334(2): 92–6. [CrossRef]
36. Holder BM, Ledbetter C. Fever of unknown origin: an evidence-based approach. Nurse Pract 2011; 36(8): 46–52. [CrossRef]
37. Sipahi OR, Senol S, Arsu G, Pullukcu H, Tasbakan M, Yamazhan T, et al. Pooled analysis of 857 published adult fever of unknown origin cases in Turkey between 1990-2006. Med Sci Monit 2007; 13(7): CR318–22.

38. Tan Y, Liu X, Shi X. Clinical features and outcomes of patients with fever of unknown origin: a retrospective study. BMC Infect Dis 2019; 19(1): 198. [CrossRef]
39. 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.
40. Baymakova M, Popov GT, Andonova R, Kovaleva V, Dikov I, Plochev K. Fever of unknown origin and Q-fever: a case series in a Bulgarian hospital. Caspian J Intern Med 2019; 10(1): 102–6.
41. Kabapy AF, Kotkat AM, Shatat HZ, Abd El Wahab EW. Clinico-epidemiological profile of fever of unknown origin in an Egyptian setting: A hospital-based study (2009-2010). J Infect Dev Ctries 2016; 10(1): 30–42.
42. Fletcher TE, Bleeker-Rovers CP, Beeching NJ. Fever. Medicine 2017; 45(3): 177–83. [CrossRef]
43. Fernandez C, Beeching NJ. Pyrexia of unknown origin. Clin Med (Lond) 2018; 18(2): 170–4. [CrossRef]
44. Brown M. Pyrexia of unknown origin 90 years on: a paradigm of modern clinical medicine. Postgrad Med J 2015; 91(1082): 665–9. [CrossRef]
45. Mulders-Manders CM, Pietersz G, Simon A, Bleeker-Rovers CP. Referral of patients with fever of unknown origin to an expertise center has high diagnostic and therapeutic value. QJM 2017; 110(12): 793–801.
46. 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. [CrossRef]
47. Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: a clinical approach. Am J Med 2015; 128(10): 1138.e1–15. [CrossRef]
48. Shoji S, Imamura A, Imai Y, Igarashi A, Yazawa M, Hirahara K, et al. Fever of unknown origin: a review of 80 patients from the Shin'etsu area of Japan from 1986-1992. Intern Med 1994; 33(2): 74–6. [CrossRef]
49. Varghese GM, Trowbridge P, Doherty T. Investigating and managing pyrexia of unknown origin in adults. BMJ 2010; 341: C5470. [CrossRef]
50. Mir T, Nabi Dhobi G, Nabi Koul A, Saleh T. Clinical profile of classical Fever of unknown origin (FUO). Caspian J Intern Med 2014; 5(1): 35–9.
51. Petersdorf RG, Larson E. FUO revisited. Trans Am Clin Climatol Assoc 1983; 94: 44–54.
52. Larson EB, Featherstone HJ, Petersdorf RG. Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970-1980. Medicine (Baltimore) 1982; 61(5): 269–92. [CrossRef]
53. Tal S, Guller V, Gurevich A. Fever of unknown origin in older adults. Clin Geriatr Med 2007; 23(3): 649–viii. [CrossRef]
54. Mahmood K, Akhtar T, Naeem M, Talib A, Haider I, Siraj-Us-Salikeen. Fever of unknown origin at a teritiary care teaching hospital in Pakistan. Southeast Asian J Trop Med Public Health 2013; 44(3): 503–11.
55. Attard L, Tadolini M, De Rose DU, Cattalini M. Overview of fever of unknown origin in adult and paediatric patients. Clin Exp Rheumatol 2018; 36 Suppl 110(1): 10–24.
56. Kucukardali Y, Oncul O, Cavuslu S, Danaci M, Calangu S, Erdem H, et al; Fever of Unknown Origin Study Group. The spectrum of diseases causing fever of unknown origin in Turkey: a multicenter study. Int J Infect Dis 2008; 12(1): 71–9. [CrossRef]
57. Zhai YZ, Chen X, Liu X, Zhang ZQ, Xiao HJ, Liu G. Clinical analysis of 215 consecutive cases with fever of unknown origin: A cohort study. Medicine (Baltimore) 2018; 97(24): e10986. [CrossRef]
58. Nield LS, Kamat DF. In: Kliegman RM, Stanton BF, St Geme JWI, Schor NF, editors. Nelson Textbook of Pediatrics. Philadelphia: Elsevier Saunders; 2015. p.1277–9.
59. Barbado FJ, Vázquez JJ, Peña JM, Arnalich F, Ortiz-Vázquez J. Pyrexia of unknown origin: changing spectrum of diseases in two consecutive series. Postgrad Med J 1992; 68(805): 884–7. [CrossRef]
60. Mulders-Manders CM, Simon A, Bleeker-Rovers CP. Rheumatologic diseases as the cause of fever of unknown origin. Best Pract Res Clin Rheumatol 2016; 30(5): 789–801. [CrossRef]
61. Bryan CS. Fever of unknown origin: the evolving definition. Arch Intern Med 2003; 163(9): 1003–4. [CrossRef]
62. Palazzi DL. Fever without source and fever of unknown origin. In: Cherry JD, Demmler-Harrison GJ, Kaplan SL, Steinbach WJ, Hotez PJ, editors. Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 7th ed. Philadelphia: Elsevier Saunders; 2014. p. 837–48.