Article received on March 25, 2020 and accepted for publishing on August 23, 2020.

VARIA

Fever of unknown origin

Gina Gheorghe[1,2], Gabriela Ceobanu[1], Florentina Gheorghe[3], Ovidiu G. Bratu[1,4], Nicolae Bacalbasa[1,5], Simona Bungau[6], Camelia C. Diaconu[1,2]

Abstract: *Fever of unknown origin (FUO) is a diagnosis that describes a prolonged febrile illness without an established cause, despite investigations. From the first definition of the medical condition (given by Petersdorf and Beeson in 1961) the diagnostic criteria have changed over time, intending to improve the management and outcome of these patients. The main causes of FUO fall into 4 categories: infectious, non-infectious (inflammatory), neoplastic and diverse causes. The etiology of FUO has changed over time, due to ever-changing disease patterns and the development of diagnostic techniques. A significant percentage of patients with FUO remain without an etiologic diagnosis, despite advanced diagnostic tests. Gathering potentially diagnostic clues through history, physical examination and nonspecific key paraclinical abnormalities is the basis for the diagnosis of FUO.*

Keywords: *fever of unknown origin, infections, malignancies, systemic inflammatory diseases*

INTRODUCTION

Fever of unknown origin (FUO) was first defined in 1961 by Petersdorf and Beeson as a medical condition that has the following three characteristics [1]:

• Body temperature 38.3° C (101° F) at three or more successive measurements.

•A duration of at least 3 weeks.

•Uncertain diagnosis after one week of hospitalization.

In the following years, the definition of FUO changed. Immunosuppressed patients were excluded from this category because they have etiological peculiarities and require a different therapeutic approach. Thus, the current definition of FUO includes the following diagnostic criteria:

•a body temperature ≥38.3°C (101°F) at least 2 determinations;

•the duration of illness for ≥ 3 weeks or recurrent febrile episodes for ≥ 3 weeks;

•the absence of immunosuppression, defined as HIV infection or known hypogammaglobulinemia, treatment with prednisone 10 mg or equivalent for a duration ≥ 2 weeks in the previous 3 months before the onset of fever, and neutropenia for a period ≥1 week 3 months before the onset of fever;

•uncertain diagnosis, despite a rigorous case history and clinical examination and the following laboratory investigations: complete blood count, erythrocyte sedimentation rate, ferritin, three blood cultures, tuberculin skin test, C-reactive protein, electrolytes, total proteins,

Corresponding author: Camelia C. Diaconu
drcameliadiaconu@gmail.com

[1] University of Medicine and Pharmacy „Carol Davila“, Bucharest, Romania
[2] Clinical Emergency Hospital of Bucharest, Bucharest, Romania
[3] Medical Center As-AIDE Sante, Bucharest, Romania
[4] Universitary Emergency Central Military Hospital, Academy of Romanian Scientists, Bucharest, Romania
[5] Department of Visceral Surgery, “Fundeni” Clinical Institute, Bucharest, Romania
[6] Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania

protein electrophoresis, creatinine, microscopic urinalysis, urine culture, creatine kinase, rheumatoid factor, antinuclear antibodies, alkaline phosphatase, lactate dehydrogenase, aminotransferases, chest X-ray, abdominal ultrasonography.

EPIDEMIOLOGY

Scientific and technological progress in the microbial diagnosis and classification of the pathogenesis of rheumatic diseases have led to a higher rate of etiological diagnosis among patients with fever. Thus, if in 1930, 75% of patients with fever had no identified causes, nowadays-true FUOs are uncommon [4, 5]. The causes of FUO vary greatly with age. Among children, the most common are viral infections, while among adults' multisystem diseases, such as rheumatic diseases or sarcoidosis, are more likely [5, 6]. Furthermore, geographical region and economic development have an important influence on the etiology of this disease. Thus, in developing countries, the most common causes of FUO are tuberculosis, typhoid fever, amebic liver abscesses and acquired immunodeficiency syndrome (AIDS). In developed countries, the travel of inhabitants to certain areas is a risk factor, resulting in the identification of rare diseases, such as malaria, filariasis, schistosomiasis, Q fever, relapsing fever, Zika virus, fever leash, etc. [5, 7]. Travelers may be infected with microorganisms to which local residents are not vulnerable, because of pre-existing immunity. The diseases contracted while abroad may have a very high incubation period, symptoms (such as fever) occurring after a period from the moment of return. This reduces the chance of an etiological diagnosis [5, 8].

A special category of patients is immunosuppressed patients, such as those with AIDS or known neutropenia. In the case of AIDS, the causes for fever are infections (79%) and malignancies (8%). In 9% of cases, the cause cannot be identified. Regarding the infectious agents, more than half of the cases were due to mycobacteria, especially atypical, the most common being the mycobacterium avium complex (MAC). Regarding malignancies among HIV-infected patients, lymphomas, particularly non-Hodgkin's lymphomas dominate [5]. Febrile episodes associated with neutropenia are most frequently caused by bacteremia, followed by the underlying disease, which has resulted in neutropenia, certain drugs, blood products, and in the case of transplanted patients, allograft rejection [5].

Usually, fever improves with an increase in neutrophils. When fever persists, although the neutrophil count has normalized, the diagnosis of hepato-splenic candidiasis can be considered [9].

ETIOLOGY

The etiology of FUO has changed over time, due to ever-changing disease patterns and the development of diagnostic techniques. The main causes of FUO fall into four categories: infectious, non-infectious (inflammatory), neoplastic and diverse causes [10]. There is also a significant percentage of cases when the etiology of fever remains unknown. A prospective multicenter study estimated the percentage of patients with FUO of 51% [11]. Over time, the frequency of malignancies and infectious diseases as causes of FUO has decreased in favor of noninfectious inflammatory diseases and cases without an etiological diagnosis [12]. From infectious diseases, the most common causes of FUO are tuberculosis and abscesses [13]. The most common malignancies presenting with fever are lymphoma, especially non-Hodgkin, leukemia, renal cell carcinoma, hepatocellular carcinoma, and liver metastasis [13]. Common noninfectious febrile inflammatory conditions correlate with patients' age. Thus, in young patients, systemic juvenile idiopathic arthritis and giant cell arteritis are frequent causes of fever [13]; in older patients, connective tissue diseases or granulomatous diseases are more frequently encountered. Table 1 presents the most common causes of FUO [10, 13, 14].

DIAGNOSIS

FUO remains a diagnostic challenge, considering that there are over 200 disorders that enter in the differential diagnosis. The diagnostic approach therefore should focus on a thorough history of the patient and finding hallmark clinical features that are characteristic of each disease, along with selective non-specific laboratory tests [13]. A detailed history of the patient can provide important diagnostic clues for FUO and should aim to orientate the paraclinical investigations necessary for the positive diagnosis [15]; it should include the history of present illness, data about recent travel, past medical history, drug history, social history and family history (Table 2) [16].

Every FUO category has clinical hallmarks the clinician should search during physical examination [15-18]. Searching potentially diagnostic clues (PDC) during the clinical exam is an important step in the diagnostic workup. PDCs are defined as "all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis"[19]:

1. Infectious diseases:
- Spinal tenderness points: suggest spinal tuberculosis, subacute vertebral osteomyelitis;
- Hepatomegaly: Q fever, typhoid/enteric fever, rat bite fever, brucellosis;

- Splenomegaly: miliary tuberculosis, Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, typhoid/ enteric fever, subacute bacterial endocarditis, Q fever;
- Regional adenopathy: characteristic of cat-scratch disease;
- Epididymo-orchitis/epididymal nodule: EBV infection, renal tuberculosis, brucellosis;
- Cutaneous findings of endocarditis: Osler nodes, Janeway lesions, splinter hemorrhages;
- Heart murmurs: suggest bacterial endocarditis.

Table 1: The most common causes of FUO.

Infections	Malignancies	Systemic inflammatory diseases	Miscellaneous
• Bacterial (tuberculosis, occult abscess, complicated urinary tract infection, osteomyelitis, Q fever, rickettsia infections, enteric fever, brucellosis) • Viral (Epstein-Barr virus, cytomegalovirus, human immuno-deficiency virus) • Parasitic (malaria, toxoplasmosis) • Fungal (histoplasmosis)	• Hepatocellular carcinoma (or liver metastasis) • Leukaemia • Lymphoma, especially non-Hodgkin's • Myelodysplastic syndromes • Multiple myeloma • Renal cell carcinoma • Sarcoma • Colon cancer • Lung cancer • Atrial myxoma	• Giant cell arteritis • Polyarteritis nodosa • Adult Still's disease • Takayasu's arteritis • Granulomatosis with polyangiitis • Mixed cryoglobulinemia • Systemic lupus erythematous • Sarcoidosis • Granulomatous hepatitis • Antiphospholipid syndrome • Behçet's disease	• Drugs (e.g. sulfone-amides, penicillin, nitrofurantoin, vancomycin, antimalarials, H1- and H2-blocking antihistamines, barbiturates, phenytoin, nonsteroidal anti-inflammatory drugs, hydralazine, methyldopa, quinidine, procainamide, anti-thyroid drugs, etc.) • Environmental (metal and polymer fume fevers) • Factitious fever • Disordered heat homeostasis • Alcoholic hepatitis • Venous thrombosis and thromboembolism • Hematoma • Hyperthyroidism and subacute thyroiditis • Pheochromocytoma • Adrenal insufficiency • Familial Mediterranean fever • Tumour necrosis factor receptor-1–associated periodic syndrome (TRAPS) • Hyper-IgD syndrome • Muckle-Wells syndrome • Familial cold autoinflammatory syndrome

2. Malignant diseases:
- Cachexia;
- Diffusely enlarged lymph nodes: lymphoma;
- Erythema nodosum: lymphoma;
- Sternal tenderness points: bone marrow disorders: preleukemia, myeloproliferative disorders;
- Eye examination: Roth spots - lymphoma, atrial myxoma; cytoid bodies - atrial myxoma; retinal hemorrhages - preleukemia.

3. Systemic inflammatory disorders:
- Skin rash: may suggest systemic lupus erythematosus (SLE), adult Still's disease [14];
- Unequal pulse: Takayasu's arteritis;
- Lacrimal gland enlargement: late-onset rheumatoid arthritis (RA), sarcoidosis, SLE;
- Oral ulcers: Behçet's disease, SLE;
- Lymphadenopathy: SLE, sarcoidosis;
- Heart murmur with negative blood cultures suggests a possible diagnosis of Libman-Sacks endocarditis.

4. Miscellaneous diseases. Miscellaneous fevers of unknown origin are often diagnosed based on historical clues rather than clinical findings. Relative bradycardia may suggest drug fever. Cirrhosis is often overlooked as a possible cause of FUO [15, 16]. Splenomegaly may be another important clue that may suggest regional enteritis, cirrhosis or hyper-IgD syndrome.

Paraclinical investigations

Before initiation of any diagnostic tests, treatments, such as antibiotics or glucocorticoids, must be stopped, as they can mask different signs and symptoms and thus delay the diagnostic process.

In any patient with FUO, the following basic laboratory tests are necessary: erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), hemoglobin, platelet count, leukocyte count and differential, electrolytes, creatinine, total protein, serum protein electrophoresis, alkaline phosphatase, aminotransferases (AST, ALT), LDH, creatine

kinase, antinuclear antibodies, rheumatoid factor, urinalysis, together with blood cultures, urine culture, a tuberculin skin test or Interferon-Gamma Release Assays (IGRA), and imaging studies - chest X-ray, abdominal ultrasonography [19].

Table 2: Key clues to FUO derived from history.

Infectious Diseases	Malignant disorders	Systemic inflammatory diseases	Miscellaneous Disorders
Prior/invasive procedures or surgeries (abscess)	Significant weight loss (2 lbs/week)	Arthralgias	Fever periodicity (cyclic neutropenia)
Dentition (apical abscesses, subacute bacterial endocarditis)	Anorexia	Myalgias	History of lymphadenopathy (Rosai-Dorfman, Kikuchi's disease)
Antecedent/concomitant infections	Post-hot bath pruritus	Dry cough (Giant cell arteritis)	Neck/jaw pain (subacute thyroiditis)
Animal/pet contact (Q fever, brucellosis, toxoplasmosis etc.)	History of adenopathy	Visual disturbances (Giant cell arteritis)	Inflammatory bowel disease (regional enteritis)
Mosquito/tick exposure (malaria, babesiosis)	History of malignancy	Acalculous cholecystitis (SLE, peri-arteritis nodosa)	Alcoholism (cirrhosis)
Rodent exposure (leptospirosis, rat bite fever)	Pel-Ebstein fever-week long high fevers with week-long remissions (Hodgkin disease)	Family history of systemic inflammatory diseases	Medications (drug fever)
Blood transfusions (CMV, HIV)	-	Jaw claudication (Giant cell arteritis)	Prolonged immobility, car trips, flights (thromboembolic disease)
Immuno-suppressive drugs	-	-	-
Nocturia (prostatitis)	-	-	-
High-risk sexual practices	-	-	-
Travel to an endemic area	-	-	-

Complete blood count contains often-overlooked clues, for example, leukopenia, monocytosis, lymphocytosis-relative lymphopenia, eosinophilia, basophilia, atypical/abnormal lymphocytes, thrombocytosis, and thrombocytopenia. In FUO, an isolated alkaline phosphatase elevation may be a clue for lymphoma [20, 21, 22]. Eosinophilia may suggest polyarteritis nodosa, drug fever, or visceral leishmaniasis. Low levels of hemoglobin or hematocrit may point toward occult hemorrhage or hematoma (often retroperitoneal).

After all potentially diagnostic clues retrieved from the patient's history, clinical examination and paraclinical investigations have been identified, the clinician should make a list of the most probable diagnoses; further specific investigations should be guided by these diagnoses.

If the diagnosis remains elusive, more advanced paraclinical investigations may be necessary. In patients with hepatomegaly or splenomegaly, abdominal computed tomography (CT) scan may be useful in detecting abnormalities such as adenopathy, abscesses or masses [23]. Echocardiography is important in case of suspicion of endocarditis or atrial myxoma. Positron emission tomography-computed tomography (PET-CT) scans help detect obscure infectious/neoplastic causes of FUO, for example, lymphomas, Q fever endocarditis or aortic graft infection [24]. Magnetic resonance imaging (MRI) may be useful in case of osteomyelitis. Digestive endoscopy may become necessary in case of suspicion of inflammatory bowel disease or sarcoidosis [25].

Invasive tests, such as lymph node biopsy, bone marrow biopsy, epididymal nodule biopsy, liver or ileal biopsy may have a high diagnostic yield [26-29]. However, these tests should be ordered based on narrowed diagnostic possibilities [30, 31].

TREATMENT

Treatment should be directed toward the underlying cause once a diagnosis is made. Because they may mask, delay or obscure the clinical manifestations, empirical therapeutic trials with antibiotics [32, 33], glucocorticoids, or antituberculous agents should be avoided in FUO, except in immunocompromised, neutropenic patients, in case of severe systemic illness or those with a rapid deterioration (patients with central nervous system or miliary tuberculosis or giant cell arteritis) [34, 35].

CONCLUSION

FUO remains one of the most difficult diagnostic challenges, as the differential diagnosis consists of over 200 malignant/ neoplastic, infectious, rheumatic/inflammatory, and miscellaneous disorders. It is essential for the clinician to

obtain potentially diagnostic clues through a detailed history of the patient, complete physical examination and guided paraclinical investigations. Interdisciplinary consultations may be appropriate in a majority of patients with FUO.

References:

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961;40:1–30.

2. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine (Baltimore) 2007;86:26–38.

3. Mulders-Manders C, Simon A, Bleeker-Rovers C. Fever of unknown origin. Clin Med (Lond) 2015;15(3):280–284.

4. Horowitz HW. Fever of unknown origin or fever of too many origins? N Engl J Med 2013;368:197.

5. Bor DH. Approach to the adult with fever of unknown origin. Available at https://www.uptodate.com/contents/approach-to-the-adult-with-fever-of-unknown-origin? (Last accessed on 20th March 2020)

6. Knockaert DC, Vanneste LJ, Bobbaers HJ. Fever of unknown origin in elderly patients. J Am Geriatr Soc. 1993; 41:1187.

7. Ibidapo MO, Akinyanju OO. Acute sickle cell syndromes in Nigerian adults. Clin Lab Haematol 2000; 22:151.

8. Korzeniewski K, Gaweł B, Krankowska D, Wasilczuk K. Fever of unknown origin in returning travellers. Int Marit Health. 2015;66(2):77-83.

9. Durack DT, Street AC. Fever of unknown origin: Re-examined and redefined. In: Current Clinical Topics in Infectious Diseases, Remington JS, Swartz MN (Eds), Blackwell Science, Boston 1991;35.

10. Beresford RW, Gosbell IB. Pyrexia of unknown origin: causes, investigation and management, Internal Medicine Journal 2016;46(9):1011-1016

11. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine (Baltimore) 2007; 86:26.

12. Bor DH. Etiologies of fever of unknown origin in adults. Available at https://www.uptodate.com/contents/etiologies-of-fever-of-unknown-origin-in-adults? (Last accessed on 20th March 2020)

13. Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: a clinical approach. Am J Med. 2015;128(10): 1138.e1-1138.e15

14. Iftimie, Georgiana; Stoian, Anca Pantea; Socea, Bogdan; et al.: Complications of systemic lupus erythematosus: A review, Rom J Mil Med, 121(3): 9-15, 2018

15. Cunha BA. Fever of unknown origin: clinical overview of classic and current concepts. Infect Dis Clin North Am. 2007;21:867-915.

16. Bush LM. Fever of unknown origin (FUO). Available at https://www.merckmanuals.com/professional/infectious-diseases/biology-of-infectious-disease/fever-of-unknown-origin-fuo (Last accessed on 20th March 2020)

17. Cunha CB. Infectious disease differential diagnosis. In: Cunha BA, ed. Antibiotic Essentials. 14th ed. New Delhi, India: JP Medical Publishers; 2015:475-506.

18. Cunha BA, Hage JE, Nouri Y. Recurrent fever of unknown origin: aseptic meningitis, hepatosplenomegaly, pericarditis and a double quotidian fever due to juvenile rheumatoid arthritis (JRA). Heart Lung. 2012;41:177-180.

19. Jameson JL, Kasper DL, Longo DL, et al. Harrison's Principles of Internal Medicine, 20th Edition. McGraw-Hill Education. 2018; 114-122.

20. Wang C, Armstrong D. Neoplastic diseases. In: Murray HW, ed. Fever of Undetermined Origin. Mount Kisco, NY: Futura Publishing; 1983:39-48.

21. Iliescu L, Mercan-Stanciu A, Ioanitescu S, Toma L. Hepatitis C-associated B-cell non-Hodgkin lymphoma: a pictorial review. Ultrasound Quarterly 2018;34(3):156-166.

22. Marcu DR, Ionita-Radu F, Iorga LD et al.: Vascular Involvement in Primary Retroperitoneal Tumors, Revista de Chimie, 70(2): 445-448, 2019

23. Bratu OG, Cherciu AI, Bumbu A, et al. Retroperitoneal tumors – treatment and prognosis of tumor recurrence. Rev Chim. 2019;70(1):191-194.

24. Pedersen TI, Roed C, Knudsen LS, Loft A, Skinhoj P, Nielsen SD. Fever of unknown origin: a retrospective study of 52 cases with evaluation of the diagnostic utility of FDG-PET/CT. Scand J Infect Dis. 2012;44:18-23.

25. Pallag A, Rosca E, Tit DM, et al. Monitoring the effects of treatment in colon cancer cells using immunohistochemical and histoenzymatic techniques. Rom J MorpholEmbryol. 2015; 56(3): 1103-1109.

26. Endres L, Tit DM, Bungau S, et al. Markers usefulness in the melanic metastatic celularepitops identification in the sentinel lymph node. Rev Chim. 2018;69(12):3675-3679

27. Kosmin A, Lorber B. Specific tests in the diagnosis of fever of unknown origin. In: Cunha BA, ed. Fever of Unknown Origin. New York: Informa Healthcare; 2007:159-208.

28. Ben-Baruch S, Canaani J, Braunstein R, et al. Predictive parameters for a diagnostic bone marrow biopsy specimen in the work-up of fever of unknown origin. Mayo Clin Proc. 2012;87:136-142.

29. Jha A, Sarda R, Gupta A, Talwar OP. Bone marrow culture vs blood culture in Fever of Unknown Origin. J Nepal Med Assoc. 2009;48: 135-138.

30. Zaha DC, Bungau S, Uivarosan D, et al. Antibiotic consumption and microbiological epidemiology in surgery departments: results from a single study center. Antibiotics. 2020; 9(2):81. https://doi.org/10.3390/antibiotics9020081

31. Zaha DC, Bungau S, Aleya S, et al. What antibiotics for what pathogens? The sensitivity spectrum of isolated strains in an intensive care unit. Sci Tot Environ. 2019;687:118-127. https://doi.org/10.1016/j.scitotenv.2019.06.076

32. Jinga M, Balaban VD, Ionita-Radu F, et al. Real life experience with ombitasvir/paritaprevir/ritonavir plus dasabuvir and ribavirin regimen in patients with compensated HCV cirrhosis. Gastroenterology. 2017;152(5):S1148-S1148.

33. Crisu GC, Ionita-Radu F, Costache R, et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir + dasabuvir and ribavirin regimen in patients with compensated HCV cirrhosis. Romanian Journal of Military Medicine. 2019;122(1):22-26.

34. Eiko LM, Bryan CS. Empiric therapy in fever of unknown origin: a cautionary note. In: Cunha BA, ed. Fever of Unknown Origin. New York: Informa Healthcare; 2007:229-236.

35. Abdel-Daim MM, El-Tawil OS, Bungau SG, Atanasov AG.

Applications of antioxidants in metabolic disorders and degenerative diseases: Mechanistic approach. Oxid Med Cell Longev. 2019; 2019:3 pages. https://doi.org/10.1155/2019/4179676