TPM Vol. 32, No. S4, 2025
ISSN: 1972-6325
https://www.tpmap.org/

APPROACH TO THE PATIENT WITH FEVER OF UNKNOWN ORIGIN: A DETAIL STUDY

MONA MOHAMMED ALHAZYAH[1*], NAJLA HUSSAIN ABDULLAH ALDOSSERY[1], NIDA ANWAR ALSHEEF[2], AMEERAH IBRAHEEM ALMREDEEF[3], SUKINAH HASSAN ALMUDARI[3], FATMAH ALI ALMOZAREA[3], GHADEER MOHAMMED ALSHAMMASI[3]

[1] MINISTRY OF NATIONAL GUARD - KING ABDULAZIZ - HOSPITAL NATIONAL GUARD – ALHASA - SAUDI ARABIA
[2] IMAM ABDULRAHMAN BIN FAISAL HOSPITAL - NATIONAL GUARD - DAMMAM - SAUDI ARABIA
[3] PRIMARY HEALTH CARE - NATIONAL GUARD - DAMMAM - SAUDI ARABIA

Received: April, 2025; **Revised**: June 2025; **Accepted**: July 2025; **Available Online**: July, 2025

ABSTRACT
Fever of unknown origin (FUO) remains one of the most challenging clinical entities in medicine because of its broad differential diagnosis and the absence of a single diagnostic test capable of identifying the underlying cause. Many people eventually have common disorders that show atypically, even though infections, cancers, and noninfectious inflammatory diseases make for the bulk of instances. The cornerstones of evaluation continue to be thorough history taking, regular physical examinations, and a phased diagnostic approach. The majority of FUO cases are linked to common diseases that appear atypically, despite the extensive list of possible causes. A comprehensive clinical history and physical examination are part of the diagnostic procedure, which is followed by focused investigations based on preliminary results and local epidemiology. In the end, improving diagnostic yield, lowering healthcare expenditures, and improving outcomes for patients with FUO can be achieved by sticking to a methodical approach and avoiding needless empiric therapy.
KEYWORDS: Fever of unknown origin; FUO; prolonged fever; diagnostic approach; infectious diseases; noninfectious inflammatory diseases; FDG-PET/CT.

INTRODUCTION

Fever of Unknown Origin (FUO) is a medical condition characterized by a persistent fever 38.3°C (101°F) or higher for 3 weeks or more that remains undiagnosed after an initial evaluation, including a comprehensive history, examination, and basic laboratory testing. This condition is challenging due to its broad differential diagnosis, which includes infections, malignancies, noninfectious inflammatory diseases, and miscellaneous causes. Despite the extensive list of potential causes, most FUO cases are attributed to common diseases presenting atypically. The diagnostic process involves a thorough clinical history and physical examination, followed by targeted investigations based on initial findings and local epidemiology. [1-3]

Classification of FUO:

The classification typically includes categories such as infections, noninfectious inflammatory diseases, malignancies, miscellaneous causes, and undiagnosed cases. These categories help guide the diagnostic process and management strategies for FUO. The following sections detail the classification and diagnostic considerations for FUO [Table1] [2,4-6].

Table1: Classification of Fever of Unknown Origin (FUO).

Category	Typical definition and setting	Minimum duration or investigation rule
Classic FUO	Community-acquired prolonged fever without source in a patient not recently hospitalized or immunosuppressed.	Historically, ≥ 3 weeks with ≥ 1 week of inpatient evaluation; 1991 defined as 3 outpatient visits or 3 hospital days.
Nosocomial FUO	Fever that begins ≥48 hours after hospital admission or is related to hospitalization events.	A shorter diagnostic interval is applied (often days) because the onset is in the hospital setting.

Neutropenic FUO	Occurs in patients with a neutrophil count of less than 500 cells/mm³; it is often seen in immunosuppressed patients undergoing chemotherapy, with presentation, organisms, and risks that differ from those in other settings.	Criteria use a much shorter observation window (often ~3 days) due to high risk and different workup priorities.
HIV-associated FUO	Fever in persons with HIV, where etiology varies with the degree of immunosuppression, reflects the unique infectious and non-infectious complications in this population.	Defined with shorter evaluation intervals and guided by CD4/clinical status.

Recent systematic reviews and consensus efforts recommend refining FUO frameworks to improve comparability and clinical utility. Proposals emphasize mechanistic alignment, the incorporation of epidemiologic context, and clearer, minimal diagnostic standards, while cautioning against the routine inclusion of advanced imaging as a defining criterion. A 2023 systematic review found discrepancies between investigator categorizations and ICD-10 adjustments and proposed a streamlined, mechanism-oriented classification to improve comparability across studies and guide empirical decisions. [7] A 2024 modified Delphi panel recommended incorporating geographic/travel epidemiology, updating classification criteria and initial evaluation standards, and limiting empiric therapies; panelists opposed including FDG-PET/CT in the formal diagnostic criteria. [8] Other contemporary reviews call for harmonized minimum testing, possible lowering of temperature thresholds, and selective use of PET/CT and next-generation sequencing guided by diagnostic clues rather than as routine first-line criteria. [8,9]

Clinical Assessment (Initial and diagnostic approach)

A clear definition and systematic initial assessment narrow the differential and guide testing for FUO. Core components include precise fever criteria, clarification of prior investigations, a focused but comprehensive history, and a repeated meticulous physical examination. History taking essentials (use repeated interviews to find diagnostic clues) include [9-11].

- **Travel and exposures**: recent travel, residence in endemic areas, animal or arthropod contacts, food exposures, and environmental/occupational risks.
- **Temporal features**: onset, duration, circadian pattern, response to antipyretics, and associated systemic symptoms such as weight loss, night sweats, or rigors.
- **Medications and procedures**: new drugs, recent antibiotics, immunizations, transfusions, recent surgeries or implants, and intravenous device history.
- **Infectious risks and behaviors**: sexual history, blood-borne exposures, and vaccination status.
- **Comorbidities and family history**: autoimmune disease in family, malignancy history, immunosuppression, and prior tuberculosis exposure.

Physical examination should be thorough and repeated regularly, as new clinical findings may emerge over time and provide important diagnostic clues [11,12].

- **General inspection** should focus on identifying cachexia, rigors, skin rashes, mucosal lesions, and potential oral or dental sources of infection.
- **Lymph node** examination is essential to assess the size, distribution, and consistency of lymphadenopathy, which may suggest infectious processes or lymphoproliferative disorders.
- **Organomegaly:** Evaluation for hepatomegaly and splenomegaly can provide clues to hematologic malignancies, infectious diseases, or granulomatous conditions.
- **Skin and mucous membranes** may reveal vasculitis lesions, petechiae, erythema nodosum, or evidence of cutaneous infections.
- **Fundoscopic** examination should be performed when clinically indicated to identify signs of infective endocarditis or opportunistic infections.
- **Joints** for arthritis or synovitis may point toward noninfectious inflammatory diseases or septic arthritis.
- **Cardiac** auscultation is crucial for detecting new murmurs that may raise suspicion for infective endocarditis and warrant further evaluation with blood cultures and echocardiography.

Pattern recognition of fever can provide etiologic clues but is rarely diagnostic on its own; integrate patterns with history and objective findings. Common fever patterns are described in FUO literature and should be documented during history-taking [10,13].

- **Continuous fever**: sustained temperature with minimal daily variation; seen in some bacterial infections, typhoid, or drug fevers
- **Remittent fever**: daily temperature fluctuations without returning to normal; common in certain infections and subacute bacterial processes.

- **Intermittent fever**: febrile episodes separated by normal temperatures; classic for malaria, some bacterial abscesses, and periodic fever syndromes.
- **Hectic fever**: high fevers with wide swings, often associated with severe infections or sepsis.
- **Relapsing or Pel-Ebstein pattern**: cyclic fevers (periods of fever then afebrile intervals), historically associated with Hodgkin lymphoma and some parasitic infections though not specific.
- Document temperature charts and antipyretic responses; patterns should steer specific testing but not replace systematic evaluation

A staged laboratory approach reduces unnecessary tests while capturing common and treatable causes. Begin with broad screening (tier 1) and proceed to targeted second-line tests when initial studies are unrevealing or clues emerge [Figure 1] [1,10,11,14].

Figure (1): Laboratory and tiered testing (Tier 1 & 2).

Tier 1 baseline tests (Minimum Initial Panel)
Routine labs: CBC with differential, ESR, CRP, basic metabolic panel, liver function tests, and urinalysis with culture.
Use repeated testing and serial inflammatory markers (ESR/CRP) to assess trend and guide escalation
Microbiology: at least three sets of blood cultures (drawn during febrile episodes) and urine cultures when indicated.
Serology and screening: HIV testing, basic viral serologies as guided by exposure risk, thyroid function tests, and protein electrophoresis if malignancy suspected.
Autoimmune screen and markers: ANA, rheumatoid factor, ANCA, LDH, ferritin (esp. when adult-onset Still's disease, HLH or malignancy suspected)
Tier 2 targeted tests (Based On Clues Or Persistent FUO)
Specific infectious serologies: EBV, CMV, Brucella, Bartonella, Coxiella burnetii (Q fever), Lyme disease and regionally relevant agents per exposure history.
Tuberculosis testing: tuberculin skin test or interferon-gamma release assays (IGRA) and directed imaging when TB exposure or risk factors exist.
Special hematologic tests: ferritin, peripheral smear review, and consideration of bone marrow aspiration/biopsy when cytopenias, suspected hematologic malignancy, or hemophagocytic syndromes are present.
CNS or focal testing: lumbar puncture when meningeal signs or neurologic symptoms are present.
Cardiac evaluation: transthoracic and transesophageal echocardiography when endocarditis is suspected after positive blood cultures or new murmur

Imaging is integral in FUO when history and labs fail to provide a diagnosis; FDG-PET/CT has emerged as a high-value whole-body tool to localize occult inflammatory, infectious, or malignant foci. Tissue diagnosis remains the definitive step when a focal abnormality is identified [2,11,14-16].

- **Chest radiograph**: initial screen for pulmonary or mediastinal processes.
- **Ultrasound**: abdominal or targeted ultrasound for hepatosplenic lesions, abscesses, biliary disease or vascular bedside assessment.
- **CT chest/abdomen/pelvis**: detailed anatomic evaluation for occult abscesses, malignancy, lymphadenopathy, and organ pathology; commonly used after baseline tests.
- **MRI**: superior for specific soft-tissue, CNS, or musculoskeletal evaluation when clinically indicated.
- **FDG-PET/CT**: whole-body functional imaging that frequently localizes occult sites of inflammation, infection, or malignancy and can guide biopsy; recommended when noninvasive tests are unrevealing and ESR/CRP are elevated.
- **Nuclear scans**: gallium and labeled leukocyte scans remain useful in selected situations but have largely been superseded by FDG-PET/CT in many centers.
- Invasive diagnostics and indications; pursue targeted invasive procedures toward abnormalities localized by imaging or persistent objective findings rather than blind generalized invasive testing: [1,11,16]
    - **Biopsy**: excisional or core biopsy of accessible abnormal lymph nodes, liver, bone marrow, temporal artery (when giant cell arteritis suspected), or other lesions when imaging/localization permits; tissue diagnosis has relatively high yield and is the preferred invasive test.

- **Bronchoscopy or endoscopy:** indicated when pulmonary or GI mucosal lesions are suspected based on imaging or end-organ clues.

CONCLUSION

Fever of unknown origin continues to pose a complex diagnostic challenge that requires a structured, patient-centered approach. Although infections, malignancies, and noninfectious inflammatory diseases account for the majority of cases, many patients ultimately have common conditions presenting atypically. Careful history-taking, repeated physical examinations, and a staged diagnostic strategy remain the cornerstones of evaluation. Investigations should be guided by clinical and epidemiological clues rather than indiscriminate testing, while invasive procedures should be reserved for patients with objective findings that warrant tissue diagnosis. Emerging diagnostic modalities, particularly FDG-PET/CT and molecular techniques, have improved the ability to identify occult causes but should complement rather than replace fundamental clinical assessment. Ultimately, maintaining a systematic approach and avoiding unnecessary empiric therapies can enhance diagnostic yield, reduce healthcare costs, and improve outcomes in patients with FUO.

Conflict of Interest: The authors state that they have no financial and others conflicts of interest.

Author contributions: The first drafts of the work are written by the original author and the cross-ponding author's supervisor. Each author contributed to the essay, collected data, edited it, created tables, and received permission to submit it to a journal for publication.

Acknowledgement: For their open access publications, the authors are grateful to Google Scholar, PubMed, DOAJ, BMJ Clinical Evidence, Embase, Medline, Cochrane Library, national and international testing laboratories.

Ethical Approval: Not Applicable

REFERENCES

1. David A, Quinlan JD: Fever of unknown origin in adults. American family physician. 2022, 105:137-143.
2. Knockaert D, Vanderschueren S, Blockmans D: Fever of unknown origin in adults: 40 years on. Journal of internal medicine. 2003, 253:263-275.
3. Kasten MJ: Chapter 6 - Fever of Unknown Origin. A Rational Approach to Clinical Infectious Diseases. Temesgen Z (ed): Elsevier, Philadelphia; 2022. 79-90. https://doi.org/10.1016/B978-0-323-69578-7.00006-5
4. Lambertucci JR, de Ávila RE, Voieta I: Fever of unknown origin in adults. Revista da Sociedade Brasileira de Medicina Tropical. 2005, 38.
5. Roth AR, Basello GM: Approach to the adult patient with fever of unknown origin. American Family Physician. 2003, 68:2223-2229.
6. Kim EJ: Fever of Unknown Origin: An Overview of the Diagnostic Approach. Korean J Med. 2021, 96:101-109. 10.3904/kjm.2021.96.2.101
7. Wright WF, Wang J, Auwaerter PG: Investigator-determined categories for fever of unknown origin (FUO) compared with International Classification of Diseases–10 classification of illness: a systematic review and meta-analysis with a proposal for revised FUO classification. In Open Forum Infectious Diseases. Volume 10. Oxford University Press US; 2023:ofad104.
8. Wright WF, Stelmash L, Betrains A, et al.: Recommendations for updating fever and inflammation of unknown origin from a modified Delphi consensus panel. In Open Forum Infectious Diseases. Volume 11. Oxford University Press US; 2024:ofae298.
9. Minamimoto R: Optimal use of the FDG-PET/CT in the diagnostic process of fever of unknown origin (FUO): a comprehensive review. Japanese Journal of Radiology. 2022, 40:1121-1137.
10. Hayakawa K, Ramasamy B, Chandrasekar PH: Fever of Unknown Origin: An Evidence-Based Review. The American Journal of the Medical Sciences. 2012, 344:307-316. https://doi.org/10.1097/MAJ.0b013e31824ae504
11. Bleeker-Rovers CP, Vos FJ, de Kleijn EMHA, et al.: A Prospective Multicenter Study on Fever of Unknown Origin: The Yield of a Structured Diagnostic Protocol. Medicine. 2007, 86.
12. Campañá VR, Paneque REJ, Silva HMR: Diagnostic utility of clinical and epidemiologic features in fever of unknown origin. The European Research Journal. 2019, 5:928-938.
13. Esposito AL, Gleckman RA: A Diagnostic Approach to the Adult With Fever of Unknown Origin. Archives of Internal Medicine. 1979, 139:575-579. 10.1001/archinte.1979.03630420061019
14. Hersch EC, Robert C: Prolonged febrile illness and fever of unknown origin in adults. American family physician. 2014, 90:91-96.

15. Kouijzer IJ, Bleeker-Rovers CP, de Geus-Oei L-F: Nuclear medicine imaging of fever of unknown origin. Nuclear Medicine in Infectious Diseases. Springer; 2019. 199-211.
16. de Kleijn EMHA, van Lier HJJ, van der Meer JWM, the Netherlands FUOSG: Fever of unknown origin (FUO): II. Diagnostic procedures in a prospective multicenter study of 167 patients. Medicine. 1997, 76.