INTERNAL MEDICINE

Cite as: Archiv EuroMedica. 2026. 16; 2. DOI [10.35630/2026/16/Iss.2.4](10.35630/2026/16/Iss.2.4)

Received 26 January 2026;
Accepted 25 March 2026;
Published 6 April 2026

FEVER OF UNKNOWN ORIGIN: ETIOLOGY, DIAGNOSTIC CHALLENGES, AND THE ROLE OF [^{18}F]FDG PET/CT

Magdalena Rumin[1], Dominika Gosztyła[2,3], Amanda Abramowicz[1], Natalia Muzyka[4], Kacper Kość[5], Gabriela Panek[1], Weronika Bukwald[4], Jakub Giersz[6], Adam Prusek[7], Remigiusz Piliński[1]

[1] Military Institute of Aviation Medicine, Warsaw, Poland
[2] Private Medical Practice, Bydgoszcz, Poland
[3] 10th Military Clinical Hospital with Polyclinic, Bydgoszcz, Poland
[4] Military Institute of Medicine, Warsaw, Poland
[5] Kazimierz Pułaski University of Technology and Humanities, Radom, Poland
[6] 4th Military Clinical Hospital with Polyclinic, Wrocław, Poland
[7] 5th Military Clinical Hospital with Polyclinic, Kraków, Poland

download article (pdf)

mada.rumin@gmail.com

ABSTRACT

BACKGROUND

Fever of Unknown Origin remains one of the most difficult diagnostic problems in internal medicine and infectious diseases. Despite advances in laboratory diagnostics and imaging technologies, establishing the cause of prolonged unexplained fever often requires extensive investigation and in a considerable proportion of patients the etiology remains unidentified. In addition, the etiological spectrum of FUO has changed over time, with increasing recognition of autoimmune, inflammatory, and neoplastic disorders alongside infectious diseases. These changes require continuous reassessment of diagnostic strategies and the integration of modern imaging and molecular diagnostic methods.

OBJECTIVE

This review aims to summarize current data on the etiological spectrum of Fever of Unknown Origin and to analyze contemporary diagnostic approaches with particular attention to the role of hybrid metabolic imaging using [^{18}F]FDG PET/CT. The review also considers differences in diagnostic evaluation between adult and pediatric patients.

METHODS

A narrative literature review was performed using the PubMed database. Publications related to the etiology and diagnostic evaluation of Fever of Unknown Origin were searched using predefined keywords including fever of unknown origin, FUO, diagnostic approach, etiology, FDG PET/CT, nuclear imaging, inflammation of unknown origin, and pediatric FUO. The search included English language articles published between 2018 and 2025. After screening and full text assessment, 40 publications including clinical studies, reviews, meta analyses, and selected case reports were included in the qualitative analysis.

RESULTS

Recent studies demonstrate that the etiological structure of FUO is heterogeneous and varies across populations and healthcare settings. Infectious diseases remain a major cause of FUO, while autoimmune, inflammatory, and neoplastic disorders represent an increasingly important proportion of cases. Hybrid imaging with [^{18}F]FDG PET/CT shows high diagnostic sensitivity for detecting metabolically active infectious, inflammatory, and malignant lesions and may reveal pathological processes not visible with conventional anatomical imaging. The integration of metabolic imaging with laboratory testing and molecular diagnostic techniques contributes to more comprehensive diagnostic evaluation in patients with prolonged unexplained fever.

CONCLUSIONS

Fever of Unknown Origin remains a complex diagnostic condition that requires a systematic and multidisciplinary diagnostic approach. Hybrid metabolic imaging with [^{18}F]FDG PET/CT represents an important diagnostic tool for identifying metabolically active disease processes and may assist in guiding further diagnostic procedures such as targeted biopsy. The combination of careful clinical assessment, conventional laboratory and imaging methods, and modern molecular diagnostic techniques may improve the diagnostic evaluation of FUO. Further research is needed to optimize diagnostic strategies and to better define the role of advanced imaging methods in clinical algorithms for FUO.

Keywords: fever of unknown origin, FUO, FDG PET/CT, nuclear medicine, molecular diagnostics

INTRODUCTION

Fever of Unknown Origin (FUO) has long been a complex and intriguing challenge in medicine. Despite advances in diagnostic methods and imaging technologies, establishing a quick and accurate diagnosis remains difficult, time-consuming, and costly [1]. FUO is recognized as a heterogeneous clinical condition that rarely has a single, clear cause. Clinical practice shows that a detailed medical history is crucial for guiding further investigation and can double the likelihood of reaching a diagnosis (72% vs. 30%). Diagnostic strategies depend on whether the underlying mechanism is infectious, inflammatory, autoimmune, or neoplastic [2].

The first definition of FUO was proposed in 1961 by Petersdorf and Beeson: fever exceeding 38.3°C for more than three weeks, with no established cause after one week of hospital evaluation. Today, FUO is more commonly defined as fever ≥ 38.0°C lasting at least eight days without an identified source, following an initial outpatient or inpatient assessment [3]. Modern clinical practice and advancements in diagnostics indicate the need to update these definitions. Revised classifications take into account both outpatient evaluation and persistent fever of at least three weeks, as well as the absence of a diagnosis after comprehensive standard testing [1].

Most patients present with nonspecific symptoms, and laboratory and imaging findings are often inconclusive, making classification exceptionally challenging. A large international study across 21 countries demonstrated that 10–30% of cases remain undiagnosed, regardless of differences in diagnostic resources [3]. The study also revealed geographic variations in FUO etiology: autoimmune and malignant causes predominate in high-income regions, while infections such as tuberculosis and brucellosis are more common in lower-income settings [4].

FUO diagnosis is further complicated by the limitations of classical imaging. Computed tomography (CT), magnetic resonance imaging (MRI), radiographs, and ultrasound mainly reveal anatomical abnormalities and provide limited insight into inflammatory or metabolic tissue activity. Therefore, clinicians have sought diagnostic methods that combine anatomical and functional imaging. In recent years, hybrid imaging techniques, particularly [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT), have gained significant importance in the diagnostic evaluation of FUO [1].

PET/CT enables whole-body imaging and identifies areas of increased glucose metabolism associated with inflammation, infection, and malignancy. Owing to its high sensitivity and diagnostic reliability, PET/CT is increasingly considered a key component of modern FUO diagnostic algorithms. It significantly shortens the time to diagnosis and reduces unnecessary procedures, including invasive tests [1,2]. Numerous studies have confirmed that incorporating PET/CT markedly improves diagnostic accuracy compared with conventional imaging [4].

The rapid development of metabolic imaging highlights the need for updated, standardized FUO diagnostic protocols.

RELEVANCE

Fever of Unknown Origin represents a persistent diagnostic challenge in internal medicine and infectious diseases. Despite substantial progress in laboratory diagnostics, microbiological testing, and imaging technologies, establishing the underlying cause of prolonged fever frequently requires extensive and time consuming investigation, and in a considerable proportion of patients the etiology remains unidentified. Large international studies demonstrate that approximately 20 to 30 percent of FUO cases remain without a definitive diagnosis even after comprehensive diagnostic evaluation using contemporary diagnostic tools [1,3].

The clinical importance of this problem is further reinforced by the evolving etiological spectrum of FUO. While infectious diseases historically represented the predominant cause of prolonged unexplained fever, recent studies indicate a growing contribution of autoimmune, inflammatory, and neoplastic disorders in both adult and pediatric populations [3,4]. This shift complicates the diagnostic process and requires adaptation of traditional diagnostic strategies to contemporary clinical realities.

Another important limitation of current diagnostic practice is the restricted ability of conventional anatomical imaging methods to detect early inflammatory or metabolically active pathological processes. Ultrasound, computed tomography, and magnetic resonance imaging primarily reveal structural abnormalities and may fail to identify hidden infectious or inflammatory foci in the early stages of disease [1,27]. These diagnostic limitations underline the clinical relevance of developing and integrating more sensitive diagnostic strategies that combine classical clinical assessment with modern imaging and molecular diagnostic technologies.

SCIENTIFIC NOVELTY

The novelty of this review lies in the structured synthesis of recent clinical evidence on the changing etiological spectrum of Fever of Unknown Origin and the evolving role of hybrid metabolic imaging in its diagnostic evaluation. The article integrates data on classical diagnostic pathways with emerging diagnostic approaches, including hybrid imaging, molecular diagnostics, and genetic technologies, reflecting the growing complexity of FUO diagnostics in contemporary clinical practice [1,21,22].

Particular attention is given to the diagnostic value of [^{18}F]FDG PET/CT in identifying metabolically active infectious, inflammatory, and neoplastic processes that may remain undetected using conventional anatomical imaging methods. Recent studies demonstrate that hybrid metabolic imaging significantly improves the detection of underlying causes of FUO and may shorten the diagnostic pathway in patients with prolonged unexplained fever [27,28].

In addition, the review comparatively examines the application of these diagnostic strategies in both pediatric and adult populations and discusses their potential integration into modern FUO diagnostic algorithms. This integrative perspective provides an updated overview of contemporary diagnostic approaches and highlights the growing role of hybrid metabolic imaging in improving the detection of underlying causes of prolonged unexplained fever.

AIM

The aim of this narrative review is to summarize the current knowledge on the etiology of Fever of Unknown Origin and to examine contemporary diagnostic strategies used in clinical practice, with particular attention to the diagnostic role of hybrid imaging with [^{18}F]FDG PET/CT in patients with FUO.

Research objectives

1. To describe the current etiological spectrum of Fever of Unknown Origin in pediatric and adult populations.
2. To outline the classical diagnostic approach to FUO and to identify its main limitations in modern clinical practice.
3. To examine the diagnostic role of modern imaging techniques, with emphasis on [^{18}F]FDG PET/CT in the evaluation of FUO.
4. To review the potential contribution of molecular diagnostic methods and inflammatory biomarkers in the diagnostic assessment of FUO.
5. To discuss existing challenges in the diagnostic workup of FUO and perspectives for improving standardized diagnostic strategies.

METHODS

STUDY DESIGN

This study was conducted as a narrative review aimed at summarizing current evidence on the etiology and diagnostic approaches to Fever of Unknown Origin and examining the role of modern diagnostic technologies, particularly hybrid imaging with [18F]FDG PET/CT, in contemporary clinical practice.

Literature search strategy

A literature search was performed in the databases PubMed, PubMed Central, and Google Scholar. The search focused on publications related to the etiology, diagnostic evaluation, and imaging approaches in Fever of Unknown Origin. The following keywords and combinations were used: fever of unknown origin, FUO, diagnostic approach, etiology, FDG PET/CT, nuclear imaging, inflammation of unknown origin, and pediatric FUO. The search was limited to articles published in English between 2018 and 2025.

STUDY SELECTION

A total of 87 publications were initially identified through the PubMed database search using predefined keywords related to Fever of Unknown Origin, diagnostic approaches, and hybrid imaging. After screening the titles and abstracts, 29 publications were excluded because they were not directly related to the diagnostic evaluation or etiology of Fever of Unknown Origin, focused on unrelated clinical conditions, or represented editorials, letters, or conference abstracts.

The remaining 58 articles were assessed in full text for relevance to the objectives of this review. During this stage, 18 publications were excluded because they contained limited diagnostic information, duplicated data already presented in other included studies, or did not contribute additional clinically relevant evidence regarding modern diagnostic strategies for FUO.

INCLUSION CRITERIA

Publications were included if they met the following criteria:

1. Studies addressing the etiology, diagnostic evaluation, or clinical management of Fever of Unknown Origin.
2. Studies examining the role of diagnostic imaging methods, particularly hybrid imaging with [18F]FDG PET/CT.
3. Publications involving adult or pediatric populations with prolonged unexplained fever.
4. Original clinical studies, systematic or narrative reviews, meta analyses, and selected case reports providing clinically relevant diagnostic insights.
5. Articles published in peer reviewed journals between 2018 and 2025 in the English language.

EXCLUSION CRITERIA

Publications were excluded if they met one or more of the following criteria:

1. Articles not related to the diagnosis or etiology of Fever of Unknown Origin.
2. Studies focusing exclusively on diseases with already established diagnoses unrelated to FUO.
3. Publications without sufficient clinical or diagnostic information relevant to the objectives of this review.
4. Conference abstracts, editorials, letters to the editor, and non peer reviewed publications.

DATA SYNTHESIS

The selected publications were analyzed qualitatively. Evidence was grouped according to major thematic areas including the etiological spectrum of FUO, classical diagnostic algorithms, modern imaging techniques, and emerging molecular and laboratory diagnostic tools. The synthesis focused on identifying current diagnostic patterns, limitations of existing approaches, and potential directions for improving diagnostic evaluation in patients with prolonged unexplained fever.

INCLUDED LITERATURE

As a result of the selection process, a final set of 40 publications was included in the qualitative analysis. These comprised review articles, original clinical studies, meta analyses, and illustrative case reports relevant to contemporary diagnostic strategies and the evolving role of hybrid imaging in FUO diagnostics.

RESULTS

ETIOLOGY OF FEVER OF UNKNOWN ORIGIN

Classification of FUO Causes – Etiological Aspects

The etiology of FUO is highly diverse and varies significantly across age groups. In children and adolescents, infectious causes dominate; however, autoimmune conditions, connective tissue diseases, chronic inflammatory disorders, malignancies, and even idiopathic origins also form an important part of the FUO spectrum, which includes more than 200 potential diagnoses [2]. In adolescents, autoimmune and connective tissue diseases occur more frequently than in younger children, emphasizing the increasing role of inflammatory etiologies in this population.

Observations in adults show a slightly higher rate of malignancy detection within one year of the initial presentation among patients who were not diagnosed with cancer at the onset of fever [2]. This suggests that in some cases FUO may represent an early manifestation of neoplastic disease before other symptoms become apparent.

The large ID-IRI (international research initiative) international project, which analyzed FUO across 21 countries, found that infections remain the most common cause (approximately 50%). Remarkably, the overall etiological distribution was similar among participating countries despite differences in healthcare resources and access to diagnostic technology. Another important finding was the consistently high proportion of undiagnosed cases—around 20%—even with contemporary diagnostic tools. This highlights the universal challenges of FUO and underscores the need for a more standardized diagnostic approach [4].

Autoimmune diseases are reported more frequently in developed countries, while malignancies also account for an increasing share of FUO cases. These trends further support the need for innovative diagnostic tools such as PET/CT.

As diagnostic technology continues to advance, it is likely that more currently unexplained cases will eventually be attributed to specific causes. This does not imply that FUO as a clinical entity will disappear but rather that earlier and more accurate diagnoses will reduce the proportion of cases labeled as idiopathic. The primary goal of modern FUO research is therefore to integrate clinical, laboratory, and imaging data into unified diagnostic pathways, creating protocols that can be applied consistently across healthcare systems [4]. The distribution of the major etiological categories of classical Fever of Unknown Origin in adults according to the international ID-IRI study is summarized in Table 1.

Table 1. Major Etiological Categories of FUO in Adults – ID-IRI Study [3]

Etiological Category	(%)	Examples / Clinical Notes
Infections	51,6	Tuberculosis, brucellosis, endocarditis, organ abscesses, viral infections
Neoplasms	11,4	Lymphomas, leukemias, organ-specific cancers
Autoimmune and Inflammatory Diseases	9,3	Systemic lupus erythematosus, vasculitis, Still's disease
Other Causes	7,6	Drugs, metabolic disorders, thrombosis, hemophagocytic syndrome
Undiagnosed	20,1	No definitive cause identified after comprehensive diagnostics

The distribution of predominant etiological causes of Fever of Unknown Origin across different age groups is presented in Table 2.

Table 2. Comparison of FUO Etiology in Children, Adolescents, and Adults

Age Group	Predominant FUO Causes	Frequency (%)

Children (<14 years)	Bacterial and viral infections	~50–60
Adolescents (14–21 years)	Autoimmune diseases, connective tissue inflammations	~25–35
Adults (>21 years)	Infections	51,6
Adults (>21 years)	Neoplasms	11,4
Adults (>21 years)	Autoimmune diseases	9,3

Erdem H, Baymakova M, Alkan S, et al. Classical fever of unknown origin in 21 countries with different economic development: an international ID-IRI study. Eur J Clin Microbiol Infect Dis. 2023;42(4):387-398. doi:10.1007/s10096-023-04561-5

FUO IN CHILDREN – ETIOLOGY AND PREDICTIVE MODELS

In the pediatric population, infectious diseases remain the most common cause of FUO, and diagnosing fever in children presents its own distinct challenges compared with adults [2,5]. Early confirmation of fever during a clinical visit is essential, as observing the child's behavior and associated symptoms during febrile episodes can provide important initial clues. Based on these observations, careful history-taking and a thorough physical examination are key components of the diagnostic process and should never be overlooked. Maintaining a home "fever diary" and, during hospitalization, a standardized fever chart, allows clinicians to assess temperature trends clearly and objectively [5].

Caregivers should be instructed on proper fever management, hydration, and the appropriate use of antipyretics, while avoiding aspirin due to the risk of Reye's syndrome. Empiric antibiotic therapy should be approached cautiously and used only when there are strong and well-supported clinical indications [3,5].

Predictive models have been developed to assist clinicians in determining the etiology of FUO and guiding decision-making. Variables such as arthritis, duration of fever, cough, splenomegaly, lymphadenopathy, anemia, and thrombocytopenia have been incorporated into such models, particularly for differentiating autoimmune diseases from malignancies, as demonstrated by AUC analysis. These models can potentially shorten diagnostic time and reduce unnecessary laboratory tests, imaging studies, and invasive procedures. However, they are not yet perfect, and further multicenter validations are required before widespread adoption [6].

A 14-year retrospective study from Singapore confirmed that arthritis and lymphadenopathy were strong predictors of connective tissue disease and necrotizing lymphadenitis. Researchers also highlighted associations between joint pain, oral ulcers, and lymphadenopathy with inflammatory or rheumatologic conditions [3]. Collecting and systematically analyzing such data may substantially improve future diagnostic algorithms for pediatric FUO. Nonetheless, despite comprehensive evaluation, a significant number of children still remain without a definitive diagnosis, reflecting the persistent complexity of FUO in this age group.

A study conducted in Beijing demonstrated that the etiology of FUO in children changes with age: infections predominate in the youngest patients, while autoimmune and neoplastic causes become more common in older children [7].

Similarly, data from Australia show that infections continue to represent the most consistent cause of FUO among hospitalized children with prolonged fever [8]. As in previous reports, the authors emphasized the importance of meticulous clinical assessment, as well as persistent use of fever diaries and fever charts [8]. They also warned against unstructured diagnostic testing performed without a clear clinical plan, as this can significantly prolong the diagnostic process—a delay that may be critical depending on the underlying etiology of FUO.

Collectively, these studies reinforce the necessity of combining detailed clinical evaluation with modern imaging and molecular diagnostic techniques to optimize etiologic identification in pediatric FUO. The etiological distribution of Fever of Unknown Origin in children based on a 14 year retrospective study is presented in Table 3.

Table 3. Etiology of FUO in Children – 14-Year Single-Center Review

Etiological Category	(%)	Examples / Clinical Notes

Infections	54,0	Typhoid fever, endocarditis, viral respiratory infections, tuberculosis
Inflammatory / Autoimmune	17,3	Kikuchi-Fujimoto disease, Still's disease, vasculiti
Hematologic / Neoplastic	6,6	Hemophagocytic lymphohistiocytosis (HLH), leukemias, lymphomas
Other / Undiagnosed	22,1	No definitive cause after comprehensive diagnostics, rare genetic and metabolic syndromes

Lim HY, Viegelmann G, Lee EY, et al. Fever of Unknown Origin in Children: A 14-Year, Single Institution Retrospective Review. Sage Open Pediatr. 2025;12:30502225251321030. Published 2025 Apr 2. doi:10.1177/30502225251321030

IMPACT OF SYMPTOM DURATION ON DIAGNOSIS

The duration of symptoms plays an important role in determining the likelihood of establishing a diagnosis in patients with FUO. A study conducted in the adult population demonstrated that the longer the fever persists, the more challenging it becomes to identify a definitive cause [9]. Notably, the probability of diagnosing malignancy decreases significantly when fever extends beyond 12 months. In contrast, patients whose fever and inflammatory symptoms lasted less than one year had a substantially higher likelihood of receiving an accurate diagnosis.

This observation highlights the importance of early, structured evaluation and close clinical monitoring. Prompt implementation of an appropriate diagnostic strategy increases the chances of identifying the underlying etiology efficiently and accurately. Early recognition is particularly crucial in conditions that may initially present with nonspecific symptoms but progress rapidly if left untreated.

RARE AND ATYPICAL CAUSES OF FUO

The study Clinical Presentation of Cat Scratch Disease in Pediatric Patients — A Single-Center Study (PMCID: PMC11562607) by Sevliya Öcal-Demir et al. highlights cat scratch disease (CSD) as one of the potential causes of FUO. Diagnosing CSD can be challenging, as it requires integrating epidemiological, bacteriological, and histological criteria. Regional lymphadenopathy—most commonly in the axillary region—may raise suspicion, especially when it progresses to suppurative, cystic changes visible on ultrasound as enlarged lobulated lymph nodes. A characteristic feature is the clinical response to azithromycin. In a cohort of 29 pediatric patients, the authors showed that CSD can present solely as FUO in a subset of cases. Although well-known, the disease may remain elusive, emphasizing the importance of asking about contact with cats, carefully palpating lymph nodes, and performing targeted ultrasound imaging [10].

Similarly, the study Cat Scratch Disease Presenting as Fever of Unknown Origin is a Unique Clinical Syndrome (Landes et al., 2020) demonstrated that CSD-related FUO most commonly affects adults with a mean age of 35.5 years, with fever lasting approximately four weeks. The researchers also described the frequency of associated extra-nodal manifestations that may guide diagnosis: hepatosplenic lesions (35%), abdominal or mediastinal lymphadenopathy, ocular involvement, and even multifocal osteomyelitis. Notably, CSD was initially misdiagnosed as malignancy in 21% of cases, and 32% of patients underwent invasive procedures before the correct diagnosis was established [11]. Altogether, these findings indicate that the combination of prolonged fever, axillary lymphadenopathy, weight loss, night sweats, and hepatosplenic abnormalities should raise suspicion for CSD-related FUO.

Another illustrative case comes from the article Brucellosis Manifesting as Fever of Unknown Origin, Septic Ankle Arthritis, and Iliacus Abscess, which describes a 61-year-old man presenting with persistent fever, abdominal pain, gastrointestinal symptoms, and anemia. Over time, he developed septic arthritis and an iliacus muscle abscess. Early microbiological and imaging studies were inconclusive, and diagnosis was delayed. Ultimately, exposure history—travel and contact with animals or unpasteurized animal products—guided clinicians toward the correct diagnosis: multi-organ brucellosis. Combined antimicrobial therapy (doxycycline with rifampicin) and abscess drainage led to full resolution of symptoms. This case reinforces the essential role of exposure-related history in evaluating FUO [12].

Another report, Too Hot to Handle: A Case of Fever of Unknown Origin, describes a 76-year-old man with multiple comorbidities and persistent nocturnal fever, dyspnea, and fatigue, yet without any clear localizing signs. Blood cultures were negative, and CT imaging of the chest and abdomen showed no abnormalities. Although urine cultures revealed Enterococcus faecalis and inflammatory markers (CRP, IL-6) were elevated, the source of fever remained unclear. Extensive autoimmune, rheumatologic, and even bone marrow studies were unremarkable. Temporary improvement occurred after glucocorticoids, but fever recurred when the dose was reduced. Ultimately, FDG-PET/CT revealed metabolically active lymphadenopathy in the abdomen and groin, raising suspicion of malignancy. The final diagnosis was high-grade diffuse large B-cell lymphoma (DLBCL) with hepatic and splenic involvement. Despite initiation of steroid therapy and combination chemotherapy, the patient developed cardiac and renal complications. This case emphasizes that aggressive hematologic malignancies remain an important cause of FUO, even when initial laboratory tests and imaging findings are normal. It also highlights the important diagnostic value of PET/CT [13].

Another example involves an immunocompetent patient presenting with an 11-day fever and right upper-quadrant abdominal pain accompanied by weight loss, decreased appetite, nausea, and vomiting. Initial suspicion focused on a tick-borne infection, and doxycycline was administered without improvement. Laboratory tests showed leukocytosis, thrombocytosis, normocytic anemia, and elevated inflammatory markers, but liver enzymes and serology for HIV (human immunodeficiency virus), EBV (Epstein-Barr virus), and CMV (cytomegalovirus) were normal. Abdominal ultrasound revealed multiple hypoechoic lesions in the right hepatic lobe, consistent with hepatic abscesses, which were confirmed on CT imaging. Aspiration identified MRSA (methicillin- resistant Staphylococcus aureus) as the causative pathogen. Several antibiotic regimens were required—including vancomycin, clindamycin, daptomycin, and linezolid combined with rifampin—along with catheter drainage of the abscesses. Only after adequate drainage did the patient's condition improve, with normalization of inflammatory markers and resolution of lesions on follow-up CT. This case demonstrates that FUO may stem from deep-seated infections with initially subtle or nonspecific findings, and that targeted imaging is crucial for diagnosis [14].

A very different scenario is presented in the article A Rare Immunological Disease: Caspase-8 Deficiency. The report describes a two-year-old child with chronic diarrhea, failure to thrive, and prolonged fever unresponsive to antibiotics and antipyretics. Both laboratory studies and imaging results appeared normal. The constellation of symptoms prompted suspicion of a primary immunodeficiency despite unremarkable routine tests. Advanced immunological and genetic analyses eventually confirmed caspase-8 deficiency, an inborn error affecting T- and B-cell function, which explained the recurrent infections and persistent fever. This case highlights the need to consider immunologic or genetic disorders in children with atypical presentations of FUO [15].

In summary, rare etiologies of FUO illustrate the breadth of diagnostic possibilities and underscore the importance of detailed history taking, thorough physical examination, and appropriately selected diagnostic tests. Recognizing atypical presentations and maintaining an open diagnostic mindset are key to identifying uncommon causes of FUO and guiding patients toward timely and accurate treatment.

DIAGNOSTICS OF FEVER OF UNKNOWN ORIGIN: A COMPARISON OF CLASSICAL APPROACHES AND EMERGING DIAGNOSTIC STRATEGIES

Classical Diagnostic Algorithm – From History to Diagnosis (version improved minimally)

Analyzing the studies discussed above, it is possible to outline the steps typically required to establish an accurate diagnosis and construct a "classical" diagnostic algorithm for FUO:

- Thorough medical history and physical examination
- Primary laboratory tests: complete blood count with differential, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), electrolytes, liver function tests (ALT/AST), creatinine, LDL, ferritin, urinalysis with culture
- Microbiological investigations: serology (EBV, CMV, HIV), PCR testing, cultures of body fluids, exposure-specific tests (Brucella, Bartonella)
- Imaging studies: chest X-ray, abdominal ultrasound, abdominal CT (second-line), MRI (when higher tissue resolution is required)
- Invasive procedures: lymph node biopsy, bone marrow biopsy, endoscopy, puncture/aspiration of focal lesions

Although this algorithm is coherent and systematic, it is time-consuming and may lead to unnecessary tests that offer little benefit to the patient. It also has several important limitations:

- Low predictive value for hidden or metabolically active foci (ultrasound, CT and MRI primarily depict anatomy and may miss small inflammatory lesions)
- Non-specific or false-negative laboratory results (e.g., lack of leukocytosis or negative cultures does not exclude early-phase inflammation)
- The full algorithm is time- and cost-intensive if applied to every patient

- Cultures may be negative in individuals receiving prior antibiotic therapy
- Limited access to specialized teams capable of performing biopsies or punctures in some centers

In summary, the classical diagnostic algorithm is effective when the disease provides clear anatomical or metabolic clues that help direct further evaluation. However, its usefulness becomes limited when such findings are subtle or absent, which often prolongs the diagnostic process. The comparison of classical diagnostic approaches and emerging modern methods used in the evaluation of Fever of Unknown Origin is presented in Table 4.

Table 4. Classical vs. Modern Approaches to FUO Diagnostics

Diagnostic Stage / Method	Classical Approach	Modern Directions
History and Physical Examination	Fundamental role in guiding further investigations. Assessment of general and local symptoms, exposures, travel history, medications, and comorbidities.	Remains foundational, increasingly supported by digital tools, clinical decision support algorithms, and EHR data analysis.
Laboratory and Microbiological Tests (Primary) [16,17]	CBC, CRP, ESR, blood and urine cultures, liver function tests, basic imaging (US, CT) – essential components of FUO workup.	Expanded with molecular tests (PCR, mNGS, 16S rRNA), cytokine profiles, biomarkers (e.g., procalcitonin, IL-6), and broad serological panels.
Conventional Imaging [18]	Ultrasound, CT, MRI targeted to suspected infection or malignancy sites; often performed sequentially.	Hybrid imaging: [^{18}F]FDG PET/CT – integrates metabolic and anatomical imaging, detecting inflammatory or neoplastic foci not visible on CT.
Invasive Procedures / Biopsies [19]	Lymph node, bone marrow, liver biopsies, and fluid aspirations performed after non-invasive methods fail.	Improved targeting of biopsies guided by PET/CT or mNGS, including image-guided biopsies with high sensitivity.
Limitations / Challenges [20]	Difficulty detecting hidden foci, false-negative results, prolonged diagnostic time, high hospitalization costs.	New methods are promising but require validation, standardization, remain costly, and have limited availability. Prospective studies are needed.

Abbreviations: CBC-complete blood count; CRP- C-reactive protein; ESR- erythrocyte sedimentation rate; PCR- polymerase chain reaction; mNGS- metagenomic next-generation sequencing; 16S rRNA-16S ribosomal ribonucleic acid, IL-6- interleukin-6, MRI- magnetic resonance imaging, [^{18}F]FDG PET/CT-[^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography

INNOVATIVE MOLECULAR AND GENETIC TOOLS

Although the classical diagnostic algorithm is often sufficient, in some cases the evaluation of a patient with FUO becomes far more complex and requires the use of advanced molecular and genetic technologies.

One of the methods increasingly considered in such situations is whole-exome sequencing (WES), used to identify genetic abnormalities that may underlie certain conditions presenting with fever of unknown origin. This approach has demonstrated that the etiology of FUO may extend beyond infectious, inflammatory, or malignant causes, and in selected cases may have a genetic basis. Research has shown that WES can substantially redirect the diagnostic pathway in patients whose standard laboratory and imaging results remain inconclusive. However, the method is associated with significant costs, requires careful interpretation by trained specialists, and depends on close collaboration between clinicians and clinical geneticists. Nevertheless, many authors strongly recommend incorporating WES into the diagnostic algorithm, particularly when traditional methods fail to establish a diagnosis

[21].

Another promising tool is metagenomic next-generation sequencing (mNGS), which has been evaluated for the detection of microbial causes of FUO, especially in children with hematological malignancies. In these studies, blood samples collected 1–31 days after fever onset were analyzed using mNGS, alongside inflammatory markers such as IL-6, a potential indicator of bacterial infection. In nearly 50% of cases, the pathogen identified through mNGS proved to be the actual cause of fever. Importantly, most patients whose treatment was subsequently modified experienced clinical improvement. Elevated IL-6 levels were strongly associated with bacterial infections, supporting its value as a complementary marker that enhances the diagnostic performance of mNGS. Overall, the results indicate that mNGS is a highly useful tool for identifying infectious causes of FUO, particularly in immunocompromised individuals [22].

Research has also examined the possible role of chromosomal abnormalities in the etiology of FUO. A study conducted in a pediatric population in China demonstrated that chromosomal irregularities may have a significant impact on diagnostic and therapeutic decisions, especially when standard clinical algorithms fail to provide an explanation for prolonged fever. These findings reinforce the need for a multidimensional diagnostic approach, particularly in children with persistent fever and negative microbiological results. Genetic testing can serve as an important complement to classical diagnostic methods in these challenging cases [23].

In summary, modern molecular and genetic technologies highlight the complexity of FUO and the necessity of integrating multiple diagnostic perspectives. The ongoing development of these tools enables clinicians to refine the diagnostic process, minimize invasive procedures, and consider etiologies that would otherwise remain undetected. When used appropriately, they serve as valuable extensions to the classical diagnostic algorithm, offering a broader and more comprehensive view of the underlying causes of FUO.

IMAGING STUDIES – HOW DIAGNOSTIC APPROACHES HAVE EVOLVED OVER THE YEARS

The main imaging techniques used in the diagnostic evaluation of Fever of Unknown Origin and their principal characteristics are summarized in Table 5.

Table 5. Comparison of Imaging Diagnostics Over Time

Method	Historical Role and Characteristics	Contemporary Use / Development	Advantages	Limitations
USG [24]	Since the 1970s, primary imaging modality in FUO for detecting liver, kidney, and lymph node lesions.	Increasingly used for vascular assessment (e.g., Takayasu disease) and real-time monitoring of inflammatory lesions.	Non-invasive, inexpensive, radiation-free, bedside availability.	Limited sensitivity for deep lesions, operator-dependent.
CT	Since the 1980s, gold standard for localizing abscesses, tumors, and inflammatory lesions.	Currently combined with contrast and 3D reconstruction, enabling detection of inflammatory and neoplastic lesions.	High resolution, widely available.	Ionizing radiation, limited functional assessment.
MRI	Initially reserved for CNS; since the 1990s included in FUO diagnostics.	Used for evaluating bone marrow, parenchymal organs, and soft tissue inflammation without radiation.	High soft tissue sensitivity, no radiation exposure.	Long examination time, high cost, contraindications (implants, claustrophobia).

PET/CT [18]	Since 2000 – integration of metabolic and anatomical imaging; breakthrough for FUO, especially inflammatory and neoplastic causes.	Currently the most sensitive method for detecting inflammatory and neoplastic foci; enables early FUO diagnosis.	Combines metabolic and anatomical data; high predictive value; reduces diagnostic time.	High cost, limited availability, requires specialist interpretation.
mNGS [21,23]	Innovative technique – developed over the past decade; previously lacked methods for detecting non-culturable pathogens.	Currently applied in FUO diagnostics (especially in immunocompromised patients), often integrated with biomarkers (e.g., IL-6).	Detects pathogens missed by conventional methods; improves diagnostic accuracy; reduces time to diagnosis.	High cost, requires bioinformatics interpretation, lack of full standardization.

The comparison presented in Table 5 illustrates how modern diagnostic strategies complement the classical FUO workup. The integration of clinical assessment, laboratory investigations, and advanced imaging methods allows a more targeted and efficient diagnostic approach in patients with prolonged unexplained fever.

BIOCHEMICAL AND INFLAMMATORY MARKERS

Imaging studies are not the only important tools in the diagnostic evaluation of FUO. Biochemical and inflammatory markers also play a key role, particularly in situations where no clear infectious focus or structural abnormalities are visible on imaging. The article "Biochemical and inflammatory markers in patients investigated for fever of unknown origin (FUO): diagnostic role and differentiation of sarcoidosis" highlights the usefulness of these markers in the diagnostic workup of sarcoidosis. The most relevant indicators include ACE (angiotensin-converting enzyme), which reflects disease activity, and CHIT1 (chitotriosidase), which has been shown to be more sensitive and specific than ACE. Additional inflammatory markers such as CRP, ESR, and leukocyte count provide complementary information. The combined assessment of CHIT1 and ACE considerably improves diagnostic accuracy and may significantly shorten the time needed to establish a diagnosis. CHIT1, in particular, shows promise as a future biochemical standard in suspected granulomatous diseases. Elevated ACE and CHIT1 are more suggestive of sarcoidosis, whereas increased CRP and IL-6 tend to indicate an infectious etiology [25].

The integration of biochemical markers with PET/CT and molecular techniques such as PCR or mNGS represents a promising direction for modern FUO diagnostics.

In the study "Usage of Plasma Presepsin, C-Reactive Protein, Procalcitonin and Mid-Regional Pro-Adrenomedullin to Predict Bacteremia in Febrile Neutropenia of Pediatric Hematological-Malignancy Patients", the authors focused on children with febrile neutropenia following treatment for hematologic malignancies. The biomarkers evaluated included presepsin, procalcitonin (PCT), MR-proADM (Mid-Regional Pro-Adrenomedullin), and CRP, with the aim of assessing their value in predicting bacteremia. The strongest individual predictors were presepsin and MR-proADM. According to the authors, a combined panel including presepsin, PCT, MR-proADM, and CRP may substantially accelerate diagnostic decision-making, particularly in high-risk pediatric patients in whom rapid intervention is crucial. However, further research is required before such a panel can be incorporated into standard FUO diagnostic protocols [26].

In summary, biochemical markers can provide essential guidance in the diagnostic approach to FUO. Although some of these tests may be costly and not widely accessible, they offer valuable opportunities to shorten the diagnostic process and improve accuracy, especially when combined with modern imaging and molecular methods.

ROLE OF [^{18}F]FDG PET/CT IN FUO DIAGNOSTICS

Mechanism and Principles

FDG Function:

Fluorodeoxyglucose labeled with the ^18F isotope (FDG) is a glucose analog—structurally similar to glucose but carrying a radioactive ^18F marker. The isotope emits positrons (+), which, after annihilation with electrons (−) in the body, produce two gamma photons traveling in opposite directions. These photons are registered by the PET detector.

FDG accumulates in tissues with increased glucose metabolism, such as inflammatory lesions or malignant tumors.

Step-by-Step FDG PET/CT Procedure

Preparation:

The patient must be fasting and avoid physical activity before the examination to minimize non-specific metabolic uptake that could compromise image quality.

FDG Administration:

FDG is injected intravenously, followed by an uptake period of about 60 minutes, allowing the tracer to distribute and enter metabolically active cells.

Imaging:

The PET/CT scan provides both functional and anatomical information:

- PET detects gamma photons from radioactive decay, creating a map of metabolic activity,
- CT provides detailed anatomical images for accurate localization.

Interpretation:

Regions of increased FDG uptake may indicate neoplastic lesions or sites of active inflammation. Importantly, elevated uptake does not necessarily imply malignancy.

Cellular Mechanism

FDG enters cells via glucose transporters (e.g., GLUT). Once inside, it is phosphorylated to FDG-6-phosphate, which cannot proceed further through glycolysis and cannot leave the cell. This metabolic “trapping” enables visualization of pathologically active tissue on PET imaging.

Limitations of PET/CT

- Increased FDG uptake is not specific to cancer; it may also reflect inflammation, tissue repair, or recent muscular activity.
- Uptake patterns may vary depending on the time between tracer injection and imaging.
- When PET findings influence treatment decisions, histopathological confirmation may still be necessary.

DIAGNOSTIC PERFORMANCE AND STUDY OUTCOMES

FDG-PET/CT consistently demonstrates higher sensitivity and overall diagnostic performance compared with conventional imaging modalities. In most studies, its sensitivity reaches approximately 85–90%, whereas standard CT typically identifies only 60–70% of clinically relevant findings. A key strength of PET is its ability to reveal metabolically active lesions—including inflammatory, autoimmune, and neoplastic processes—with particularly high accuracy in conditions such as vasculitis and lymphomas. Equally important is the diagnostic value of a negative PET/CT result: the absence of FDG-avid foci strongly argues against an active infectious, inflammatory, or malignant process and can markedly shorten the diagnostic work-up.

The clinical usefulness of PET/CT increases further when results are interpreted alongside inflammatory markers such as CRP, ESR, ferritin, and IL-6. Although PET/CT is considered a highly informative tool, it is most often used as a second-line or adjunctive modality, largely due to its cost, limited availability, and the need for expert interpretation[19]. Similar conclusions are presented in the study 18F-FDG PET/CT for Identifying the Causes of Fever of Unknown Origin (FUO), which emphasizes the value of PET/CT even at earlier diagnostic stages. By highlighting foci of abnormal metabolic activity, PET/CT helps narrow the diagnostic pathway and guides further targeted investigations. The authors underline, however, that PET/CT is meant to complement standard imaging—not replace it—and that further prospective studies are needed to define precisely at which point in the FUO algorithm it should be used as a first-line versus second-line examination [27].

A large single-center study (Diagnostic Value of F-18 FDG PET/CT in Fever or Inflammation of Unknown Origin) confirmed the method's significant impact on clinical decision-making. Among 300 evaluated patients, PET/CT was decisive in 162 cases (54%). In 72 patients, it directly prompted a new therapeutic intervention, while in 54 cases it led to modification of ongoing treatment. Interestingly, CRP and leukocyte counts did not consistently correlate with PET findings, demonstrating that inflammatory markers may have limited predictive value in selected scenarios [28]. Another study reported a higher diagnostic yield of PET/CT in inflammation of unknown origin (IUO) than in classic FUO, indicating that PET/CT may be particularly valuable when an inflammatory etiology is suspected rather than applied indiscriminately in every case of persistent fever [29].

Impact of FUO Definition on Diagnostic Accuracy

The diagnostic accuracy of PET/CT also depends on how strictly FUO is defined. Broad or non-specific FUO criteria may reduce predictive value, potentially leading to both over- and underestimation of infectious causes. Refining patient selection—based on fever duration, exclusion of known etiologies, and standardized clinical assessment—can meaningfully improve diagnostic yield and reduce unnecessary negative results [30].

Evolution of Nuclear Medicine in FUO

Nuclear medicine continues to evolve rapidly, and its role in FUO diagnostics is expanding. Incorporating PET/CT into diagnostic algorithms significantly increases the detection of etiologies that remain inconspicuous on traditional imaging. Improvements in scanner resolution, shorter acquisition times, and more sensitive detectors have made PET/CT increasingly accessible and reliable. Nonetheless, limitations remain: high cost, limited availability, and radiation exposure all require thoughtful patient selection. Future directions include whole-body metabolic screening integrated with molecular diagnostics, as well as the growing use of artificial intelligence for image interpretation, which may further enhance diagnostic [31].

PET/CT in Pediatric Populations

In children, classical diagnostic pathways can be challenging due to atypical symptom presentation and difficulties in obtaining a complete medical history. PET/CT offers whole-body, non-invasive metabolic imaging, reducing the need for repeated or invasive procedures. However, more research is needed to establish pediatric-specific protocols that incorporate nuclear medicine into FUO diagnostics [32]. The principal nuclear medicine imaging techniques used in the diagnostic evaluation of Fever of Unknown Origin and their main characteristics are summarized in Table 6.

Table 6. Comparison of PET/CT and SPECT/CT (e.g., 99mTc-UBI) in FUO diagnostics

Technique	Mechanism	Advantages	Disadvantages	Applications
$[^{18}F]$FDG-PET/CT [27]	Detects increased glucose metabolism in inflammatory and neoplastic tissues	High sensitivity (>85%); can localize both infectious and neoplastic lesions; integrates metabolic and anatomical imaging	Low specificity (physiological uptake in muscles, brain, heart); high cost; radiation exposure	FUO diagnostics in children and patients with central nervous system disorders; early clinical research phase.
SPECT/CT	Imaging using gamma isotopes (e.g., ^{99m}Tc, ^{111}In) – detects inflammatory activity	Combines functional and anatomical data; widely available; lower cost than PET/CT	Lower spatial resolution; longer scan time; limited sensitivity for small or deep lesions	Diagnosis of bone, joint, and prosthetic infections; endocarditis; complements PET/CT
^{99m}Tc-UBI (ubiquicidin) [33]	Radiotracer binds directly to bacterial membranes – differentiates	High specificity for bacterial infections; rapid blood clearance; early	Limited availability; no widespread clinical standardization;	Differentiating bacterial infection vs. sterile inflammation in

	infection from sterile inflammation	detection of infection sites	few prospective studies	FUO; complements PET/CT
Gallium-67 citrate (^{67}Ga)	Accumulates in sites of inflammation and tumors via binding to transferrin and lactoferrin	Good availability; can assess systemic infections (e.g., sarcoidosis, endocarditis)	Long accumulation time (48–72 h); low resolution; high radiation exposure	Rarely used now; still useful in countries with limited PET access
PET/MRI (^{18}F-FDG) [31]	Hybrid combination of PET and MRI – metabolic and morphological imaging with lower radiation	Better soft tissue contrast than PET/CT; reduced radiation; more precise localization of CNS lesions	High cost; long scan time; limited availability; requires advanced interpretation	FUO diagnostics in children and patients with CNS disease; early clinical research phase

Abbreviations: SPECT/CT- single-photon emission computed tomography/ computed tomography; ^{99m}Tc-UBI (ubiquicidin)- technetium-99m-labeled ubiquicidin; Gallium-67 citrate (^{67}Ga)- gallium-67 citrate; PET/MRI (^{18}F-FDG)- positron emission tomography/ megnetic resonance imaging using [^{18}F]fluorodeoxyglucose

These data demonstrate that hybrid metabolic imaging with FDG PET CT currently represents the most sensitive modality in FUO diagnostics, while other nuclear medicine techniques such as SPECT CT or infection specific radiotracers may serve as complementary approaches in selected clinical situations.

The development of nuclear medicine techniques has made it possible to combine functional imaging with precise anatomical assessment. Recent studies consistently identify F-18 FDG PET/CT as a non-invasive and highly effective diagnostic tool in FUO. At the same time, radiotracer techniques based on ^{99m}Tc-UBI may gain increasing relevance in the future, particularly for the detection of bacterial infections, where their specificity could complement or enhance FDG-based imaging [33].

NEW TECHNOLOGIES AND THE FUTURE OF PET/CT

Long Axial Field-of-View (LAFOV) PET/CT and Emerging Radiotracers

Long Axial Field-of-View PET/CT (LAFOV) enables substantially shorter acquisition times while requiring lower radiotracer doses. This improvement increases patient comfort and safety and expands the feasibility of PET/CT in groups that traditionally pose diagnostic challenges—critically ill patients, pregnant women, and children.

New tracers, including FAPI (fibroblast activation protein inhibitor) and CXCR4-targeted agents, show promise in reducing the number of false-positive FDG findings by providing greater specificity for certain inflammatory or neoplastic pathways. Authors highlight that further research is needed to establish standardized protocols, clarify clinical indications, and identify additional safe and effective radiotracers. Collectively, these developments represent a transformative direction for future diagnostic strategies [34].

Guide to Image Acquisition and Interpretation

In the article State of the Art of 18F-FDG PET/CT Application in Inflammation and Infection: A Guide for Image Acquisition and Interpretation, the authors emphasize several key elements essential for obtaining reliable and reproducible PET/CT results.

Patient preparation plays a critical role: a minimum 60-minute uptake period after radiotracer injection is recommended; blood glucose levels should be within normal limits; and adequate hydration must be ensured. Avoiding brown fat activation is particularly important, as it can create artifacts and decrease diagnostic accuracy.

Standardization of acquisition parameters is equally crucial. For suspected systemic disease, full-body imaging—from head-to-toe or skull-to-mid-thigh—is recommended.

Image interpretation incorporates both visual and quantitative criteria: tracer distribution patterns, asymmetry, and comparison with physiological background, as well as numerical parameters such as SUV and TBR. Clinicians must also remain aware of common diagnostic pitfalls, including physiological uptake, implant-related artifacts, and contrast effects.

The authors underscore the need for clear, unified guidelines to support the integration of FDG-PET/CT into standardized FUO diagnostic algorithms [35].

APPLICATION IN SPECIAL POPULATIONS

Pediatric, Oncological, and Immunosuppressed Populations

The study 18F-FDG PET/CT of FUO/IUO in Special Populations highlights the notably high diagnostic performance of PET/CT in pediatric FUO, as well as in patients with renal impairment, HIV infection, or those treated in intensive care units. In diagnostically ambiguous cases, PET/CT frequently provides decisive clues and often guides subsequent therapeutic decisions.

Importantly, a negative PET/CT scan also has diagnostic value, as it can reliably exclude metabolically active inflammatory or neoplastic foci. However, certain patient groups, including individuals with renal dysfunction, patients with indwelling urinary catheters, and those with HIV infection, have a higher risk of artifacts and false-negative findings due to altered tracer pharmacokinetics. These factors must be taken into account when planning and interpreting the examination. The authors emphasize the need for larger, standardized studies to enable broader implementation of PET/CT and to incorporate it into classical FUO diagnostic algorithms [36].

Practical Application of PET/CT

PET/CT enables the precise localization of infectious or neoplastic lesions and allows clinicians to assess their extent, facilitating tailored and etiology-directed treatment. The information provided by PET/CT often eliminates the need for redundant diagnostic procedures, including invasive interventions such as biopsies.

This modality is particularly useful for diagnosing rare or diagnostically challenging conditions such as sarcoidosis, vasculitis, or deep-seated infections, especially when conventional tests remain inconclusive. PET/CT is relatively safe and minimally burdensome, making it especially valuable in children, elderly patients with multiple comorbidities, and those who are immunosuppressed. Rapid and accurate diagnosis remains a cornerstone of effective FUO management.

DISCUSSION

Hybrid metabolic imaging with PET/CT has emerged as one of the most informative diagnostic tools in the evaluation of Fever of Unknown Origin. Its principal advantage lies in the ability to detect metabolically active lesions before structural abnormalities become visible on conventional anatomical imaging. This feature is particularly important in FUO, where early inflammatory, infectious, or neoplastic processes may remain undetectable using standard radiological techniques. PET/CT therefore plays a particularly important role in identifying causes of FUO associated with malignancies, systemic inflammatory diseases, and autoimmune disorders [16,18,19].

In inflammatory conditions, PET/CT is also highly useful for detecting deep or occult infectious foci. Lesions such as deep abscesses, osteomyelitis, vasculitis, or organ specific inflammatory processes may remain inconspicuous on ultrasound, computed tomography, or magnetic resonance imaging, especially in early stages of disease. By visualizing areas of increased glucose metabolism throughout the entire body, PET/CT can guide further diagnostic evaluation and help identify the most appropriate sites for targeted biopsy [14,16,18].

Compared with conventional imaging modalities, PET/CT demonstrates substantially higher diagnostic sensitivity in many clinical scenarios related to FUO. While ultrasound, CT, and MRI primarily provide structural information, PET/CT combines anatomical localization with functional assessment of metabolic activity. This integrated approach may accelerate diagnostic decision making, shorten the time required to establish the underlying cause of fever, and allow earlier initiation of targeted therapy. In addition, the identification of metabolically active lesions frequently facilitates the selection of optimal biopsy sites, which may significantly improve diagnostic accuracy [15,16,19].

The etiological structure of FUO has also evolved over time and represents an important aspect of the diagnostic challenge. Historically, infectious diseases accounted for the majority of FUO cases. However, contemporary studies demonstrate a growing contribution of autoimmune, inflammatory, and neoplastic disorders, particularly in developed healthcare settings. At the same time, the relative distribution of etiological categories varies significantly between regions and populations, reflecting differences in epidemiology, healthcare access, and diagnostic resources. This heterogeneity complicates the development of universal diagnostic algorithms and requires flexible diagnostic strategies that integrate clinical assessment with modern imaging and laboratory investigations [3,4].

Laboratory and molecular diagnostic methods remain essential complementary tools in the evaluation of prolonged unexplained fever. Inflammatory biomarkers such as C reactive protein, erythrocyte sedimentation rate, and procalcitonin may help differentiate between infectious and noninfectious causes of fever and guide further investigation. In addition, advances in molecular diagnostics, including polymerase chain reaction based pathogen detection and genomic approaches, have expanded the ability to identify infectious agents and rare inflammatory conditions that may otherwise remain undiagnosed. These methods do not replace imaging techniques but rather provide additional diagnostic information that, when interpreted together with clinical findings and imaging results, may significantly improve the diagnostic accuracy in patients with FUO [21,22].

Despite these advantages, PET/CT has several important limitations. The technique remains relatively expensive and is not universally available, particularly outside large specialized medical centers. Accurate interpretation of PET/CT findings also requires considerable expertise, as increased tracer uptake is not specific to malignant or infectious processes and may occur in various physiological or reparative conditions, including normal brain metabolism, muscular activity, or tissue healing after injury. Furthermore, the absence of fully standardized interpretation criteria contributes to variability between institutions and may influence diagnostic performance [14,20].

Another limitation concerns the current evidence base. Although numerous clinical studies support the diagnostic value of PET/CT in FUO, the number of high quality prospective investigations remains limited. As a result, diagnostic algorithms incorporating PET/CT as a routine component of FUO evaluation are not yet universally standardized. Additional multicenter prospective studies are needed to determine the optimal timing of PET/CT within diagnostic pathways and to clarify its clinical value across different age groups and etiological categories [15,18,19].

Future developments in nuclear medicine may further expand the diagnostic potential of metabolic imaging. Active research is currently focused on the development of novel radiotracers targeting specific inflammatory or neoplastic pathways. These agents may provide greater specificity than conventional [18F]FDG and could complement or partially replace current imaging strategies in selected clinical situations. Such advances have the potential to improve diagnostic precision and contribute to the development of more refined and standardized approaches to the evaluation of patients with Fever of Unknown Origin [14,20].

CONCLUSIONS

Fever of Unknown Origin remains a complex diagnostic condition, with a substantial proportion of cases remaining unresolved despite comprehensive evaluation. The etiological spectrum is heterogeneous and includes infectious, autoimmune, inflammatory, and neoplastic causes, with variations across age groups and healthcare settings.

Hybrid metabolic imaging with [18F]FDG PET/CT demonstrates high diagnostic sensitivity and represents an important tool for detecting metabolically active disease processes, particularly when conventional methods are inconclusive. Laboratory biomarkers and molecular diagnostic techniques provide additional complementary information.

An integrated diagnostic approach combining clinical assessment, targeted laboratory testing, and modern imaging is required to improve diagnostic accuracy and optimize patient management.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

Conceptualization: Remigiusz Piliński, Weronika Bukwald, Kacper Kość;

Methodology: Jakub Giersz, Adam Prusek;

Software: Gabriela Panek;

Check: Jakub Giersz, Dominika Gosztyła, Amanda Abramowicz;

Formal analysis: Adam Prusek, Natalia Muzyka;

Investigation: Weronika Bukwald, Kacper Kość, Jakub Giersz;

Resources: Magdalena Rumin;

Data curation: Natalia Muzyka, Gabriela Panek;

Writing – rough preparation: Remigiusz Piliński, Weronika Bukwald, Kacper Kość;

Writing – review and editing: Adam Prusek, Natalia Muzyka, Gabriela Panek, Dominika Gosztyła, Amanda Abramowicz, Magdalena Rumin;

Visualization: Gabriela Panek, Amanda Abramowicz;

Supervision: Magdalena Rumin;

Project administration: Remigiusz Piliński;Receiving funding: Magdalena Rumin.

All authors have read and agreed with the published version of the manuscript.

FUNDING

This research received no external funding.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Wright, W. F., Mulders-Manders, C. M., Auwaerter, P. G., & Bleeker-Rovers, C. P. (2022). Fever of Unknown Origin (FUO) - A Call for New Research Standards and Updated Clinical Management. The American journal of medicine, 135(2), 173–178. https://doi.org/10.1016/j.amjmed.2021.07.038
2. Ryan K. (2024). Fever of Unknown Origin. The Medical clinics of North America, 108(1), 79–92. https://doi.org/10.1016/j.mcna.2023.05.016
3. Erdem, H., Baymakova, M., Alkan, S., Letaief, A., Yahia, W. B., Dayyab, F., Kolovani, E., Grgic, S., Cosentino, F., Hasanoglu, I., Khedr, R., Marino, A., Pekok, A. U., Eser, F., Arapovic, J., Guner, H. R., Miftode, I. L., Poposki, K., Sanlidag, G., Tahmaz, A., … Rello, J. (2023). Classical fever of unknown origin in 21 countries with different economic development: an international ID-IRI study. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology, 42(4), 387–398. https://doi.org/10.1007/s10096-023-04561-5
4. Rupasinghe, H., Nourse, C., Robson, J., & Berkhout, A. (2025). Prolonged Fever in Children: An Inpatient Diagnostic Framework for Infections in Australia. Journal of paediatrics and child health, 61(4), 532–539. https://doi.org/10.1111/jpc.70027
5. Hu, B., Chen, T. M., Liu, S. P., Hu, H. L., Guo, L. Y., Chen, H. Y., Li, S. Y., & Liu, G. (2022). Fever of unknown origin (FUO) in children: a single-centre experience from Beijing, China. BMJ open, 12(3), e049840. https://doi.org/10.1136/bmjopen-2021-049840
6. Lim, H. Y., Viegelmann, G., Lee, E. Y., Durnford, J., Rajan, C., Chong, C. Y., Li, J., Thoon, K. C., Nadua, K. D., Kam, K. Q., Yung, C. F., Soh, S. Y., Taschawee, A., Das, L., Choo, J. T. L., Liew, W. K., & Tan, N. W. H. (2025). Fever of Unknown Origin in Children: A 14-Year, Single Institution Retrospective Review. Sage open pediatrics, 12, 30502225251321030. https://doi.org/10.1177/30502225251321030
7. Rienvichit, P., Lerkvaleekul, B., Apiwattanakul, N., Pakakasama, S., Rattanasiri, S., & Vilaiyuk, S. (2025). Prediction model for etiology of fever of unknown origin in children. European journal of pediatrics, 184(7), 429. https://doi.org/10.1007/s00431-025-06277-4
8. Trapani, S., Fiordelisi, A., Stinco, M., & Resti, M. (2023). Update on Fever of Unknown Origin in Children: Focus on Etiologies and Clinical Approach. Children (Basel, Switzerland), 11(1), 20. https://doi.org/10.3390/children11010020
9. Betrains, A., Wright, W. F., Moreel, L., Staels, F., Blockmans, D., & Vanderschueren, S. (2022). Etiological spectrum and outcome of fever and inflammation of unknown origin. Does symptom duration matter?. European journal of internal medicine, 106, 103–110. https://doi.org/10.1016/j.ejim.2022.10.002
10. Odeh, A., Alkhaled, F., & Soudi, S. (2024). Unraveling a Complex Case: Brucellosis Manifesting as Fever of Unknown Origin, Septic Ankle Arthritis, and Iliacus Abscess. Cureus, 16(11), e74147. https://doi.org/10.7759/cureus.74147
11. Pruitt, S. E., Filipek, J., Williford, D., Sanders, S., Slagle, B., Young, H., & Snowden, J. (2024). Fever of Unknown Origin: A Case Report of Hepatic Phlegmon in an Immunocompetent Patient. Cureus, 16(4), e59229. https://doi.org/10.7759/cureus.59229
12. Landes, M., Maor, Y., Mercer, D., Habot-Wilner, Z., Bilavsky, E., Chazan, B., Cohen, R., Glikman, D., Strahilevitz, J., Katzir, M., Litachevsky, V., Melamed, R., Guri, A., Shaked, H., Perets, O., Wiener-Well, Y., Stren, A., Paul, M.,

Zimhony, O., Srugo, I., … Giladi, M. (2020). Cat Scratch Disease Presenting as Fever of Unknown Origin Is a Unique Clinical Syndrome. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 71(11), 2818–2824. https://doi.org/10.1093/cid/ciz1137

13. Joshi, R. R., Hess, K. J., Sullivan, D. M., Maguire, M., & Hans, A. S. (2022). Too Hot to Handle: A Case of Fever of Unknown Origin. Cureus, 14(1), e20942. https://doi.org/10.7759/cureus.20942
14. Bazgir, N., Tahvildari, A., Chavoshzade, Z., Jamee, M., Golchehre, Z., Karimi, A., Dara, N., Fallahi, M., Keramatipour, M., Karamzade, A., & Sharafian, S. (2023). A rare immunological disease, caspase 8 deficiency: case report and literature review. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology, 19(1), 29. https://doi.org/10.1186/s13223-023-00778-3
15. Öcal-Demir, S., Kahraman, K., Bozbeyoğlu, G., & Esen, F. (2024). Clinical Presentation of Cat Scratch Disease in Pediatric Patients-A Single-Center Study. Turkish archives of pediatrics, 59(6), 574–579. https://doi.org/10.5152/TurkArchPediatr.2024.24032
16. Nozawa, H., Ogura, M., Miyasaka, M., Suzuki, H., Ishikura, K., Ishiguro, A., & Ito, S. (2021). Ultrasonography as a Diagnostic Support Tool for Childhood Takayasu Arteritis Referred to as Fever of Unknown Origin: Case Series and Literature Review. JMA journal, 4(4), 358–366. https://doi.org/10.31662/jmaj.2020-0115
17. Sun, B., Yang, M., Hou, J., Wang, W., Ying, W., Hui, X., Zhou, Q., Yao, H., Sun, J., & Wang, X. (2022). Chromosomal abnormalities related to fever of unknown origin in a Chinese pediatric cohort and literature review. Orphanet journal of rare diseases, 17(1), 292. https://doi.org/10.1186/s13023-022-02444-0
18. Zhang, P., Zhang, Z. H., Liang, J., Shen, D. Y., Li, J., Wang, D., Jin, F. F., Song, H., Zhang, J. Y., Xu, W. Q., Tang, Y. M., & Xu, X. J. (2022). Metagenomic next-generation sequencing for the diagnosis of fever of unknown origin in pediatric patients with hematological malignancy. Clinica chimica acta; international journal of clinical chemistry, 537, 133–139. https://doi.org/10.1016/j.cca.2022.10.008
19. Guo, W., Feng, X., Hu, M., Shangguan, Y., Xia, J., Hu, W., Li, X., Zhang, Z., Shi, Y., & Xu, K. (2022). The Application of Whole-Exome Sequencing in Patients With FUO. Frontiers in cellular and infection microbiology, 11, 783568. https://doi.org/10.3389/fcimb.2021.783568
20. Di Francesco, A. M., Verrecchia, E., Sicignano, L. L., Massaro, M. G., Antuzzi, D., Covino, M., Pasciuto, G., Richeldi, L., & Manna, R. (2021). The Use of Chitotriosidase as a Marker of Active Sarcoidosis and in the Diagnosis of Fever of Unknown Origin (FUO). Journal of clinical medicine, 10(22), 5283. https://doi.org/10.3390/jcm10225283
21. Agnello, L., Bivona, G., Parisi, E., Lucido, G. D., Iacona, A., Ciaccio, A. M., Giglio, R. V., Ziino, O., & Ciaccio, M. (2020). Presepsin and Midregional Proadrenomedullin in Pediatric Oncologic Patients with Febrile Neutropenia. Laboratory medicine, 51(6), 585–591. https://doi.org/10.1093/labmed/lmaa011
22. Weitzer, F., Nazerani Hooshmand, T., Pernthaler, B., Sorantin, E., & Aigner, R. M. (2022). Diagnostic value of F-18 FDG PET/CT in fever or inflammation of unknown origin in a large single-center retrospective study. Scientific reports, 12(1), 1883. https://doi.org/10.1038/s41598-022-05911-7
23. Betrains, A., Boeckxstaens, L., Moreel, L., Wright, W. F., Blockmans, D., Van Laere, K., & Vanderschueren, S. (2023). Higher diagnostic yield of 18F-FDG PET in inflammation of unknown origin compared to fever of unknown origin. European journal of internal medicine, 110, 71–76. https://doi.org/10.1016/j.ejim.2023.01.025
24. Singh, S. B., Shrestha, N., Bhandari, S., Shrestha, S., Shrestha, B., Shrestha, N., Rijal, S., Singh, R., Hess, S., Werner, T. J., Alavi, A., & Revheim, M. E. (2024). [18F]FDG PET/CT for identifying the causes of fever of unknown origin (FUO). American journal of nuclear medicine and molecular imaging, 14(2), 87–96. https://doi.org/10.62347/OQQC6007
25. Minamimoto R. (2022). Optimal use of the FDG-PET/CT in the diagnostic process of fever of unknown origin (FUO): a comprehensive review. Japanese journal of radiology, 40(11), 1121–1137. https://doi.org/10.1007/s11604-022-01306-w
26. Olianti, C., Trapani, S., Secinaro, A., & Holm Reichkendler, M. (2024). Fever of unknown origin in pediatrics: Role of nuclear medicine. The Quarterly Journal of Nuclear Medicine and Molecular Imaging, 68(1), 48–57. https://doi.org/10.23736/S1824-4785.24.03546-5
27. Wright, W. F., Kandiah, S., Brady, R., Shulkin, B. L., Palestro, C. J., & Jain, S. K. (2024). Nuclear Medicine Imaging Tools in Fever of Unknown Origin: Time for a Revisit and Appropriate Use Criteria. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 78(5), 1148–1153. https://doi.org/10.1093/cid/ciae115
28. Wright, W. F., Wang, J., & Auwaerter, P. G. (2024). Fever of Unknown Origin (FUO) Criteria Influences Diagnostic Outcomes: A Systematic Review and Meta-Analysis. The American journal of medicine, 137(12), 1246–1254.e6. https://doi.org/10.1016/j.amjmed.2024.07.015

29. Albano, D., Rodella, C., Guarneri, A., Romano Gargarella, E., & Leccisotti, L. (2025). [18F]FDG PET/CT of FUO/IUO in special populations. The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the Society of..., 69(3), 219–223. https://doi.org/10.23736/S1824-4785.25.03649-0
30. Casali, M., Lauri, C., Altini, C., Bertagna, F., Cassarino, G., Cistaro, A., Erba, A. P., Ferrari, C., Mainolfi, C. G., Palucci, A., Prandini, N., Baldari, S., Bartoli, F., Bartolomei, M., D'Antonio, A., Dondi, F., Gandolfo, P., Giordano, A., Laudicella, R., Massollo, M., … Signore, A. (2021). State of the art of 18F-FDG PET/CT application in inflammation and infection: a guide for image acquisition and interpretation. Clinical and translational imaging, 9(4), 299–339. https://doi.org/10.1007/s40336-021-00445-w
31. DI Franco, M., DI Giorgio, A., Farolfi, A., Amon, M., Mingels, C., Nardo, L., & Triumbari, E. K. (2025). A scoping review on potential of novel developments in fever of unknown origin and inflammation of unknown origin: long-axial-field-of-view positron emission tomography/computed tomography and novel radiotracers. The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the Society of..., 69(3), 224–237. https://doi.org/10.23736/S1824-4785.25.03656-8
32. Malek, H., Hedayati, R., Maghsudi, M., & Yaghoobi, N. (2023). Diagnosis of Fungal Infection (Candida albicans) After Heart Transplantation in a Pediatric Case with Fever of Unknown Origin: Role of 99mTc-UBI SPECT/CT and 18F-FDG PET/CT. Nuclear medicine and molecular imaging, 57(3), 155–158. https://doi.org/10.1007/s13139-022-00781-3
33. Roth, A. R., & Basello, G. M. (2003). Approach to the adult patient with fever of unknown origin. American family physician, 68(11), 2223–2228.
34. Wright, W. F., & Auwaerter, P. G. (2020). Fever and Fever of Unknown Origin: Review, Recent Advances, and Lingering Dogma. Open forum infectious diseases, 7(5), ofaa132. https://doi.org/10.1093/ofid/ofaa132
35. Kouijzer, I. J. E., Mulders-Manders, C. M., Bleeker-Rovers, C. P., & Oyen, W. J. G. (2018). Fever of Unknown Origin: the Value of FDG-PET/CT. Seminars in nuclear medicine, 48(2), 100–107. https://doi.org/10.1053/j.semnuclmed.2017.11.004
36. Bharucha, T., Rutherford, A., Skeoch, S., Alavi, A., Brown, M., Galloway, J., & FDG-PET/CT in fever of unknown origin working group (2017). Diagnostic yield of FDG-PET/CT in fever of unknown origin: a systematic review, meta-analysis, and Delphi exercise. Clinical radiology, 72(9), 764–771. https://doi.org/10.1016/j.crad.2017.04.014
37. Mulders-Manders, C., Simon, A., & Bleeker-Rovers, C. (2015). Fever of unknown origin. Clinical medicine (London, England), 15(3), 280–284. https://doi.org/10.7861/clinmedicine.15-3-280
38. Bleeker-Rovers, C. P., Vos, F. J., Mudde, A. H., Dofferhoff, A. S. M., de Geus-Oei, L. F., Rijnders, A. J., Krabbe, P. F. M., Corstens, F. H. M., van der Meer, J. W. M., & Oyen, W. J. G. (2007). A prospective multi-centre study of the value of FDG-PET as part of a structured diagnostic protocol in patients with fever of unknown origin. European journal of nuclear medicine and molecular imaging, 34(5), 694–703. https://doi.org/10.1007/s00259-006-0295-z
39. Horowitz H. W. (2013). Fever of unknown origin or fever of too many origins?. The New England journal of medicine, 368(3), 197–199. https://doi.org/10.1056/NEJMp1212725
40. Cunha, B. A., Lortholary, O., & Cunha, C. B. (2015). Fever of unknown origin: a clinical approach. The American journal of medicine, 128(10), 1138.e1–1138.e15. https://doi.org/10.1016/j.amjmed.2015.06.001

back