*Clinical Infectious Diseases*

STATE-OF-THE-ART REVIEW

# State-of-the-Art Review: Contemporary Ambulatory Approach to Adult Fever of Unknown Origin

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Fever of unknown origin remains a diagnostic frontier, with research predominantly focused on the underlying disease spectrum. However, this focus largely overlooked issues between previous diagnostic criteria—the "quantitative" or "qualitative" definitions—and the critical role of evaluating the patient. This review synthesizes mounting evidence that the qualitative criteria are a central, yet underappreciated, driver of an effective and efficient clinical evaluation process for the ambulatory adult immunocompetent population. With input from infectious disease physicians, rheumatologists, and oncologists with expertise in this area, we chart the complex landscape of this widely recognized and potentially devastating condition, revealing key recommendations from a modified Delphi consensus panel and the Society of Nuclear Medicine and Molecular Imaging that offer changes beyond earlier definitions and management. By recentering the conversation around this updated approach, we argue for a paradigm shift for modern clinical practice and future research.

**Keywords.** fever; fever of unknown origin; inflammation; pyrexia; pyrexia of unknown origin.

Fever of unknown origin (FUO), also known as pyrexia of unknown origin or fever of undetermined origin, remains a widely recognized and sometimes debilitating clinical condition encountered globally [1, 2]. While the incidence remains uncertain, prevalence ranged from 2.0 to 2.9% among 2 retrospective cohort studies from Japan and Italy that included 9830 hospitalized patients meeting the classic FUO criteria [3, 4]. Despite the paucity of epidemiologic data, particularly for Africa and the Americas in this century, regular encounters among patients with prolonged fevers occur among clinicians at all levels of the healthcare system in both community hospitals and university referral centers [5–10].

This condition continues to rank among the most challenging for clinicians because there has previously been no uniform criteria that patients must meet, no universally accepted evaluation method, and no agreement on a standardized classification for associated diseases [6–8]. Additionally, the prevalence of reported underlying associated diseases differs among age groups [2], geographical location [8–10], country-level gross national income per capita (GNI) [2, 11], fever pattern and duration [10], prospective or retrospective study design [2, 8, 11], differences in applied defining criteria [2], and geographic variation in healthcare services utilization over time [8].

Given certain subspecialist, such as infectious diseases, rheumatology, and oncology, may be tasked with evaluating these patients, this review aims to highlight recent advances and provide an evidence-based and practical approach to the evaluation and management of this complex clinical problem. Due to the underlying disease spectrum of prolonged unexplained fevers in children, adolescents, and immunocompromised adults, discussion is limited to immunocompetent adults with prolonged unexplained febrile conditions (ie, classic FUO) [6, 12]. In the many areas where data are lacking, expert opinion is provided.

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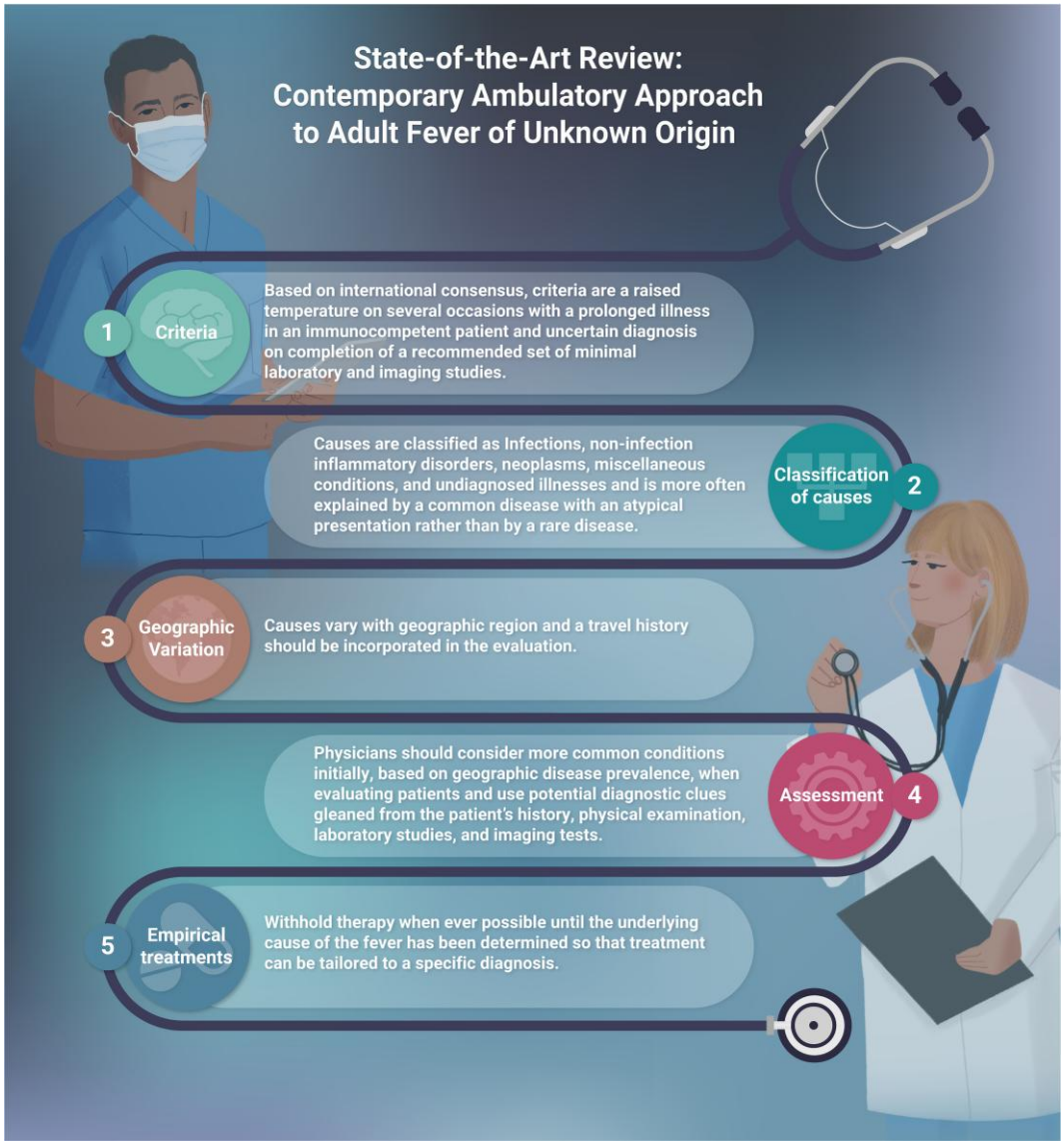


## DIAGNOSTIC CRITERIA

From 1907 to 1961, clinicians in the United States described patients with prolonged perplexing fevers with various temperature thresholds, fever durations, and intensities of evaluation [13–15]. The first formal definition to gain broad acceptance was a prospective study conducted at Yale University from 1952 to 1957 by Paul Beeson with Robert Petersdorf studying 100 consecutive patients satisfying 3 prerequisites: "*fever higher than 101.0°F (38.3°C) on several occasions, illnesses of more than three weeks duration, and diagnosis uncertain after one week of study in hospital*" [16]. Although the original 1961 definition has evolved (Table 1) [6, 10–16], a recent Delphi-generated consensus-based recommendation offers a definition adapted for modern clinical practice and future research [12]. These new criteria require more than 3 weeks fever (≥38.3°C [100.9°F] on >3 occasions) without explanation, despite completing a set of minimal standard diagnostic tests in an immunocompetent adult patient [12]. Experts strongly recommend that both researchers and clinicians use this new set of criteria, as it would improve comparability among future studies and assist in evaluating their patients [12].

## DIFFERENTIAL DIAGNOSIS

### Classification of Associated Conditions

Historical studies classified associated etiologies by infection type [13], as either established or unestablished diagnoses [14], low- or high-grade fever [15], and infections or malignant

**Table 1. Evolution of Fever of Unknown Origin Definitions**

| Publication [Ref, Year] | Diagnostic Criteria |
|---|---|
| Petersdorf and Beeson [16, 1961] | Illness of more than three weeks' (wks) duration, fever higher than 101°F (38.3°C) on several occasions, and diagnosis uncertain after one week of study in hospital. |
| Durack and Street[a] [17, 1991] | Fever ≥38.0°C, >3 wks illness and diagnosis uncertain after >2 outpatient visits or 3 days in hospital. |
| De Kleijn et al[a,b,c] [18, 19, 1997] | Fever higher than 100.9°F (38.3°C) on several occasions, illness of more than 3 wks, and diagnosis uncertain after completing a minimal set of investigations[c] in the hospital or outpatient clinic in an immunocompetent patient. |
| Wright et al[a,b] [20, 2021] | Fever higher than 100.4°F (38.0°C) on several occasions, illness of more than 3 wks, and diagnosis uncertain after completing a minimal set of investigations in the hospital or outpatient clinic in an immunocompetent patient. |
| Delphi panel[a,d] [12, 2024] | Fever higher than 100.9°F (38.3°C) on several occasions, illness of more than 3 wks, and diagnosis uncertain after completing a minimal set of investigations in the hospital or outpatient clinic in an immunocompetent patient. |

[a]Immunocompromised patients were excluded from the definitions of classic fever of unknown origin among these studies. Criteria used to define an immunocompromised patient include neutropenia (neutrophil count $<0.5 \times 10^9$/L) for at least 1 wk within 3 months prior to the start of the fever, receive immunosuppressive medications because of solid organ or hematologic stem cell transplant, known hypogammaglobulinemia, use of 10 mg prednisone or equivalent for 2 wks or more within 3 months prior to the onset of fever, uncontrolled human immunodeficiency virus (HIV) infection (CD4 < 200 cells/microliter), or patients who receive biologic therapies (eg, antitumor necrosis factor or other monoclonal antibodies).

[b]Fever of 38.3°C (100.9°F) or higher on at least 3 occasions was suggested. However, others suggested using 38.0°C as the threshold for fever of unknown origin as this is considered the standard clinical upper level of normal for either rectal or tympanic body temperature measurements.

[c]Minimal set of investigations occurred in 2 phases based upon the presence or absence of potential diagnostic clues. Blood cultures incubating for more than 1 week were suggested.

[d]The standard minimum set of investigations includes the following components: (1) laboratory tests—complete blood count (CBC) including differential, comprehensive metabolic panel (CMP) including calcium and liver function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, thyroid-stimulating hormone (TSH), rheumatoid factor (RF), antineutrophil cytoplasmic antibodies (ANCA), and antinuclear antibodies (ANA); (2) microbiology tests—blood cultures (minimal 3 sets with spacing and incubation of 5 d), urinalysis with reflex to urine culture (minimal 1 set), human immunodeficiency virus (HIV) 1/2 screening, and tuberculin skin test or interferon-gamma release assay; and (3) imaging tests—must include both abdomen ultrasonography and posteroanterior-lateral view chest plain-film or chest/abdominal/pelvic computed tomography (CT).

tumors [15]. Later categories added collagen-vascular disorders, hypersensitivity states, autoimmune diseases, miscellaneous conditions, factitious fevers, or no diagnosis [16, 17, 21, 22]. In 1995, researchers from the Netherlands introduced the *non-infectious inflammatory diseases* category that replaces the individual categories of collagen-based disorders, vasculitis, and autoimmune diseases [23]. While some researchers recently proposed an updated classification scheme that would align with the current understanding of disease mechanisms and international classification of diseases (ICD), the recent Delphi consensus recommends modern studies use 5 diagnostic disease categories to classify causes—infections, noninfectious inflammatory disorders, oncologic diseases, miscellaneous conditions, and undiagnosed illnesses [7, 12].

Recent meta-analyses have demonstrated that disease category proportions vary according to geographic location, country income classification, and applied FUO criteria [2, 7–11, 24, 25]. For example, a 2019 systematic review assessing 18 case series across 4 geographic regions (Europe, Far East, Middle East, and Southern Asia) with 3164 participants [2] reported higher proportions of infections among studies using Petersdorf and Beeson's criteria [16] and lower/upper middle-income countries in Southern Asia and Far East Asia as compared to high-income countries in Europe where noninfectious inflammatory disorders were more frequent. A 2023 retrospective study [1] involving 21 countries of differing economic status in Europe, Eastern Mediterranean, and Southeast Asia with 788 participants reported 51.6% of causes were due to infections (Figure 1). Additionally, a 2024 meta-analysis of 16 prospective studies reported a relative increase of 15.3% (95% CI: 2.3–28.3%, $P = .021$) in undiagnosed FUO proportions among studies that employed a qualitative criteria (ie, a specific minimal set of investigations must be performed before rendering the diagnosis of classic FUO) compared to 11 quantitative studies (ie, solely time-based) reporting 19.7% (95% CI: 6.0–33.4%, $P = .005$) more in adjusted infectious disease proportions [25]. This difference emphasizes the importance of using the new Delphi-generated criteria to provide a framework to aid in a clinical diagnosis, prevent premature application of FUO diagnoses due to varied evaluations in resource-limited settings, improve diagnostic stewardship, and achieve a relatively homogeneous disease population so multiple studies and populations can be compared or combined for research settings [12]. Use of these new criteria would also reduce the risk of overestimating the infectious diseases category associated with previous time-based criteria [12, 16, 17, 25].

### Common and Uncommon Contemporary Causes

The most important concept learned from this condition is that most patients are not suffering from unusual or rare diseases; instead, they more likely exhibit atypical manifestations of common illnesses [7–11, 16–19, 24, 26–29]. Additional lessons are that causes vary by age group and geographic location [2, 9, 10, 30]. For example, one recent Southeast Asian hospital-based prospective observational study involving 51 consecutive patients aged 60 years and above reported infections and neoplasms contributed to 72.6% of cases when compared to previous European series and individuals less than age 60 years [26]. Although this condition has a wide differential diagnosis, common and uncommon

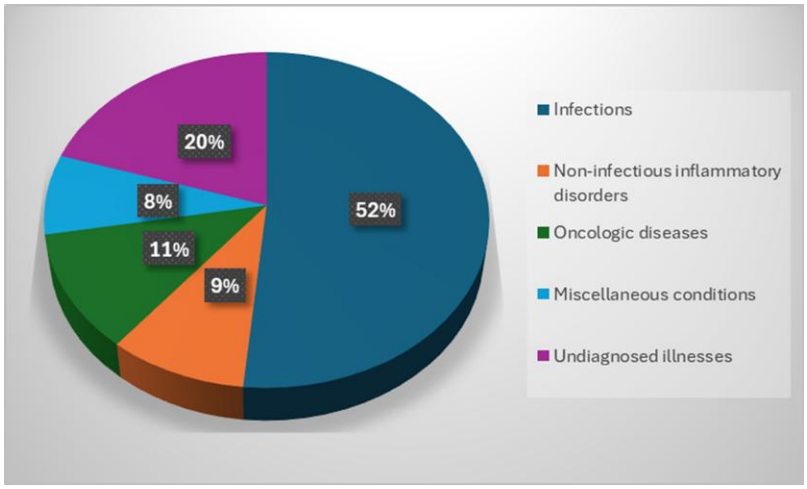


**Figure 1.** Proportions of associated disease categories among 21 countries of differing economic status with 788 participants [1]. Adapted from Erdem H, Baymakova M, Alkan S, et al. Classical fever of unknown origin in 21 countries with different economic development: an international ID-IRI study. *Eur J Clin Microbiol Infect Dis* 2023;42:387–98.

underlying contemporary causes to these categories by geographical region are listed in Figure 2 [9, 10].

Among 19 prospective studies with a total of 2667 patients and 832 infections, *Mycobacterium tuberculosis* complex (Mtb) was most commonly reported within 4 of 6 World Health Organization geographic regions (34.3%); no studies were available for Africa or the Americas [9]. Other reported infections included *brucellosis* (9.7%), endocarditis (7.5%), abscesses (7.3%), herpesvirus (eg, cytomegalovirus and Epstein–Barr virus) infections (7.2%), pneumonia (6.5%), lower and upper urinary tract infections (6.5%), and enteric fever (4.8%) [9]. Additionally, in this meta-analysis, infections were more likely from studies performed in Southeastern Asia (pooled proportion, 0.49 [95% CI, .43–.55]) than from Europe (pooled proportion, 0.31 [95% CI, .22–.41]) [9].

Of noninfectious inflammatory disorders from this same meta-analysis, 42 (7.4%) were noninfectious granulomatous conditions, 58 (10.2%) were vasculitides, and 195 (34.3%) were autoimmune and autoinflammatory disorders (defined in previous studies as collagen-vascular diseases) [10]. European studies generated more data in this category (69.2%) compared to other regions with the combined data from other countries (30.8%). Participants with collagen-vascular diseases were primarily diagnosed with Adult-onset Still disease (58.5%), systemic lupus erythematosus (26.7%), and polymyalgia rheumatica (5.6%) [10]. Eastern Mediterranean cohorts had more systemic lupus erythematosus cases recorded than any other region [10]. In this same composite, 68.9% of patients with vasculitis syndrome had giant cell arteritis, whereas the majority of the noninfectious granulomatous disease subset (61.9%) had sarcoidosis [10].

Another recent systematic review with meta-analysis encompassing 67 studies with 16 790 cases published between 2002 and 2021 reported that Adult-onset Still disease (22.8%), giant cell arteritis (11.4%), and systemic lupus erythematosus (11.1%) were the most frequent noninfectious inflammatory disorders [11]. The proportion of noninfectious inflammatory disorders was significantly higher in high-income countries (25.9% [95% CI 21.5–30.8%]) versus middle-income countries (19.5% [95% CI 16.7–22.7%]) and with a longer febrile duration and greater number of symptoms (0.011 [95% CI .003–.021]; $P$ & .01) [11].

Hematologic malignancies predominated (57.9%) among oncology-associated diseases from a 2022 meta-analysis [10]. Rates were higher among European (41.9%) and Southeast Asia studies (35.9%). Lymphomas accounted for the highest number of cases (70.1%), followed by leukemias (25.2%), multiple myeloma (3.4%), and myelodysplastic disease (1.3%) [10]. Finally, the most common miscellaneous conditions identified in this meta-analysis included drug fever (18.4%), thyroid disease (16.5%), habitual hyperthermia (10.7%), venous thromboembolism (2.9%), Addison disease (1.9%), and Dressler syndrome (1.9%) [10]. Thyroid diseases occurred across all geographical regions. Kikuchi disease presented an increased pattern across Western Pacific and Southeast Asian regions [10].

## DIAGNOSTIC APPROACH

### Multidisciplinary Approach

Given the diversity of causes and challenges associated with extrapolating existing algorithms for an individual patient, a scientific basis for evaluating patients after they fulfill FUO criteria

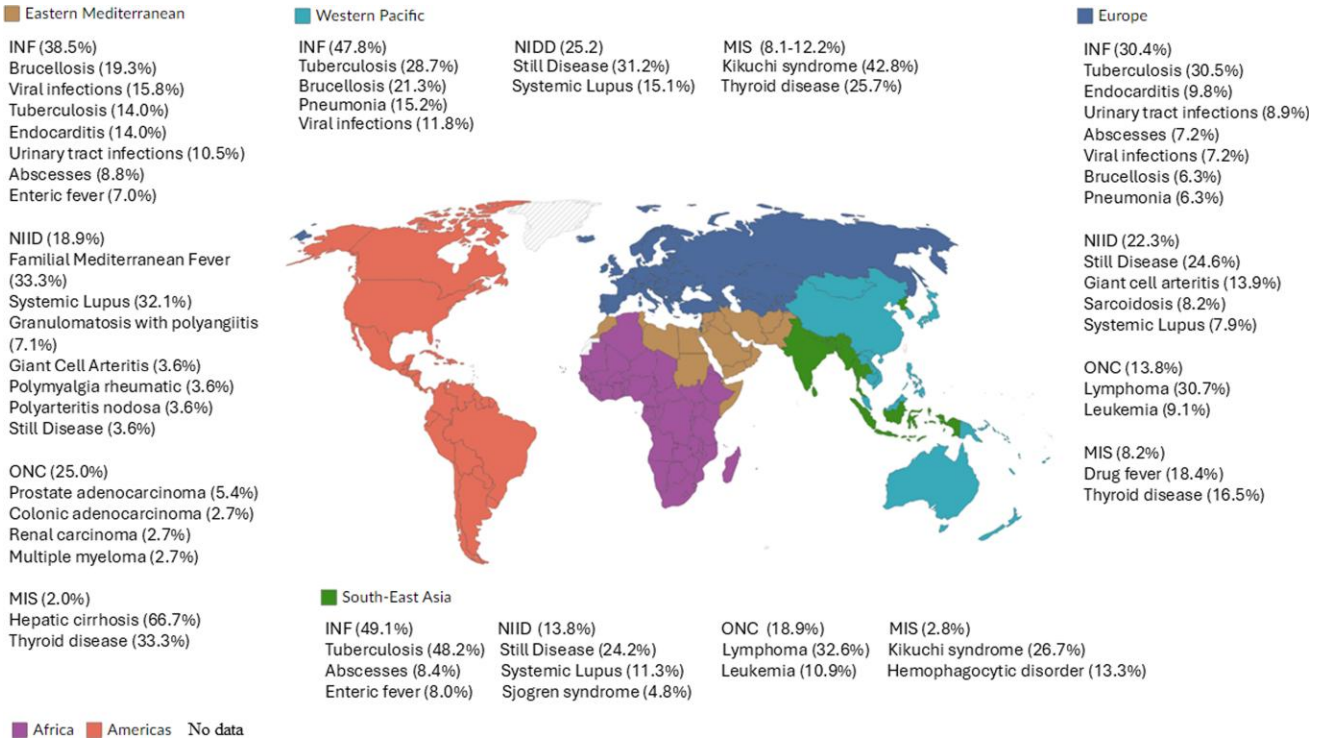


**Figure 2.** Contemporary causes based on World Health Organization geographic regions among 19 prospective studies involving 2667 patients [9, 10]. Given the lack of contemporary prospective studies, the regions of Africa and the Americas have no data. Urinary tract infections include both lower and upper tract infections. Viral infections include herpes viruses (eg, Epstein–Barr virus [EBV]; cytomegalovirus [CMV]) and other chronic viral infections (eg, hepatitis C virus [HCV]). Abbreviations: INF, infections; MIS, miscellaneous causes; NIID, noninfectious inflammatory diseases; ONC, oncologic conditions.

has been lacking [8, 12, 30]. To fill this gap, a recent Delphi consensus panel brought a consensus approach for evaluating patients with suspected FUO (Figure 3) [12, 30]. Fever of unknown origin is a complex condition best assessed and managed, if feasible, by experienced clinicians often coordinating a multidisciplinary approach. Ideally for diagnostic efficiency, this could include specialists with expertise in diagnostic pathology and laboratory medicine, infectious diseases, internal medicine, oncology, and rheumatology as necessary. Experts in radiological interventions and surgical procedural management could also be involved, particularly in cases needing invasive procedures and biopsies to establish an underlying diagnosis.

#### History and Physical Examination

While a history of rigors and shaking chills tends to be more commonly described in infectious etiologies, some suggest unintentional weight loss and early anorexia have been associated with oncologic disorders [31]. However, these features are nonspecific and should be interpreted in the broader clinical context. Therefore, a thorough history and physical examination serves as the foundation of evaluation and can be significant in determining the choice of all further investigations [16, 30]. Special consideration must be given to a patient's geographic location and social history, encompassing exposure to pets, other animals, unusual foods, work environment, and recent interactions with individuals exhibiting similar symptoms or possible disease carriers [30]. Delphi consensus panel experts recently recommended incorporating travel history [12].

The past medical history should be thoroughly assessed for previous febrile illnesses, recent infections, or new conditions like lymphoma and rheumatic fever, as well as any intraabdominal disorders that could explain the source of the fever [30]. The family history should be scrutinized for ethnic background and possible hereditary causes of fever (ie, Familial Mediterranean fever). A complete list of the patient's medications and their duration of use is required for evaluation as potential sources [30]. Finally, the diagnostic effectiveness of physical examination findings alone in assessing FUO lacks sufficient study for concrete evidence-based recommendations. Yet, it is self-evident that a careful clinical examination is key to evaluating these patients.

#### Verification of Fever and Fever Patterns

Clinicians have endeavored to diagnose diseases by analyzing associated fever (ie, a measured body temperature ≥38.3°C [100.9°F]) patterns since the earliest days of clinical

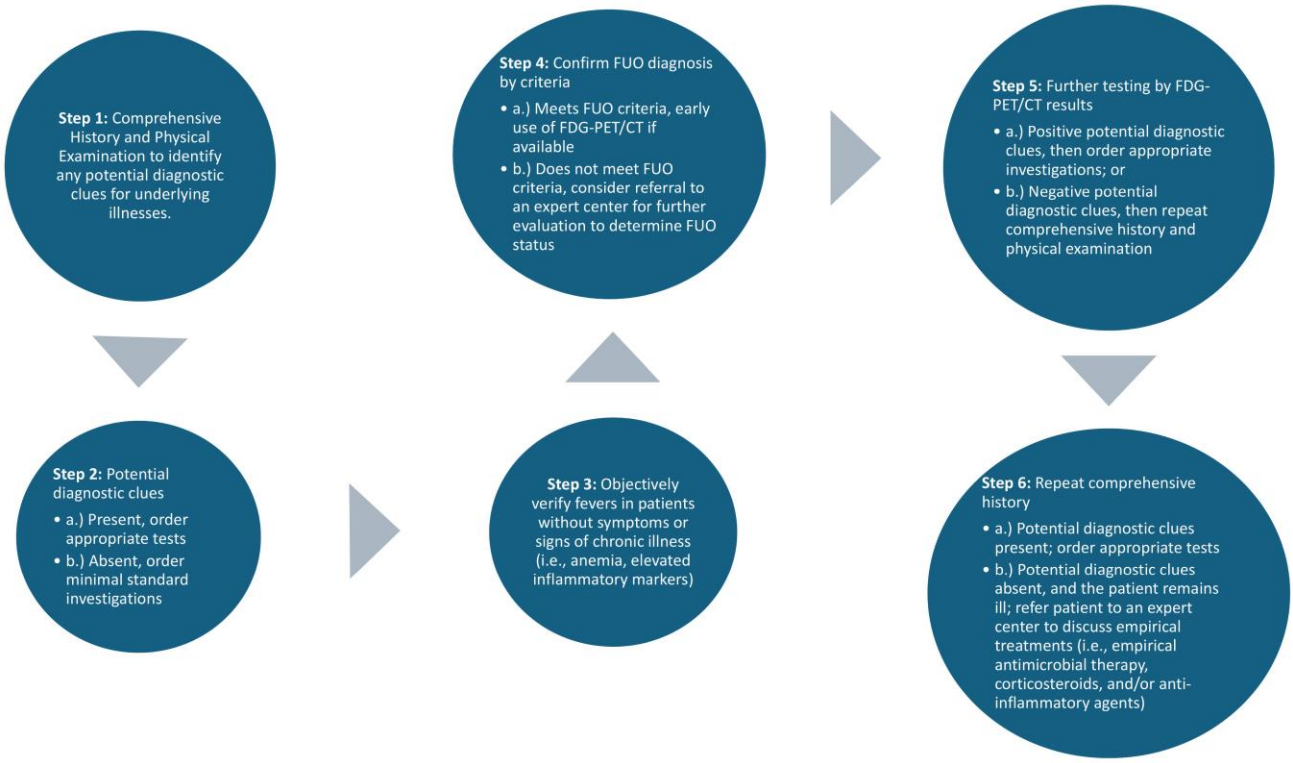


**Figure 3.** Systematic stepwise approach to suspected fever of unknown origin patient based upon the 2024 Delphi-generated recommendations [30]. Adapted from Wright WF, Durso SC, Forry C, Rovers CP. Fever of unknown origin. *BMJ* 2025;388: e080847.

thermometry [16–19, 21, 22, 32, 33]. While a few such as the well-known periodicity of tertian and quartan malaria, Pel-Ebstein pattern seen in some Hodgkin disease, typhus inversus (normal diurnal pattern reversal) in some disseminated tuberculosis, and pulse-temperature disassociation sometimes seen in typhoid fever, have been posited as having diagnostic value. However, these and other fevers patterns (remittent, intermittent, hectic, quotidian, picket fence, sustained, and saddleback) are unfortunately rarely observed and insufficient as sole identifiers of any disease [11, 32]. Furthermore, liberal use of antipyretic therapy renders fever patterns less interpretable and use of nonsteroidal anti-inflammatory drugs, the naproxen test, to differentiate neoplastic from nonneoplastic fevers lacks diagnostic value [34]. Finally, based on recent observational data, fevers present more often as a continuous (daily or nearly daily) prolonged pattern [10, 27, 28].

Although fever patterns alone are rarely diagnostically suggestive, they can occasionally provide useful information and should be considered in conjunction with other symptoms, signs, and laboratory data [10, 11, 27, 28, 32]. For example, several prospective and retrospective studies have shown that episodic fevers, at least 2 episodes of fever with fever-free intervals of at least 2 weeks not related to therapies, are often associated with causes that remain uncertain [10, 27, 28]. Patients with recurrent fevers in one study had a higher rate of undiagnosed illness (47.6–50.0%) after evaluations compared to patients with a continuous fever (20.0–25.9%) [10]. Finally, the resolution of fever after the institution of a disease-specific therapy (eg, empirical therapy for suspected tuberculosis) sometimes may provide sufficient evidence to support a presumptive diagnosis [30, 32].

Delphi consensus experts recommended the following: (1) clinicians should objectively verify fevers in the setting of patients without symptoms or signs of an underlying illness (eg, anemia of chronic illness, and/or elevated inflammatory markers such as erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) before subjecting anyone to an extensive clinical evaluation, and (2) exclude factitious fevers [12, 33]. Taking into consideration the diurnal nature of temperature, morning nadir (6–8 AM) and late afternoon peak (4–6 PM), clinicians should also instruct such patients without objective findings to keep a daily temperature log for fevers >38.3°C (>100.9°F), the site of measurement, and instrument used [11, 12]. Characteristics more likely to be associated with factitious fever include markedly elevated temperatures (>41.1°C [106.0°F]), discrepancy between simultaneous oral and rectal temperatures, lack of diurnal temperature variation, rapid defervescence, absence of tachycardia, disparity between the physical examination and temperature recording, and a history of other factitious illnesses (eg, Munchausen syndrome)

[12, 32]. To improve scientific and clinical communication in clinical investigations, experts recommend that researchers and clinicians specify the anatomical region of temperature measurement, the instrument utilized for detection, and the fever diagnosis threshold [12, 33]. While there is no agreed-upon anatomical site or instrument, contact thermometers placed on the forehead or in the mouth, ear, axilla, or rectum have traditionally been used to monitor patients' temperatures [33]. Therefore, it is important to document the site of measurement since temperature varies depending on the body site [33]. Readings obtained with non-contact infrared thermometers, which measure surface temperature (generally the mid-forehead), are influenced by numerous human, environmental, and equipment variables, all of which can affect their accuracy, reproducibility, and relationship with core temperature [35].

#### Minimal Laboratory Investigations and Potential Diagnostic Clues

Studies directly comparing the components of the current minimal laboratory investigations defining a patient as FUO are lacking [36]. While the recent Delphi consensus [12] did not advocate the use of these inclusionary criteria per se, the question of which components should be used in this role remains unanswered [35]. However, the importance of Mtb as a major cause of FUO and leading infection worldwide is noteworthy and bears out that regardless of geography, disease from this pathogen remains a prime consideration in this population [1–4, 9, 13–16, 21, 26, 30, 32]. Furthermore, a recent meta-analysis of 19 prospective studies published between 1997 and 2021 with 2667 total cases, Mtb predominated across all geographic regions (n = 285 [34.3%]) among infections [9]. Therefore, we recommend screening with either a tuberculin skin test or interferon-gamma release assay as an important minimal component of an FUO investigation [12]. If available, the interferon-gamma release assays were preferred over tuberculin skin testing by Delphi panel members as they deliver objective results unaffected by reader variability, can be performed in one visit, and are not influenced by prior Bacillus Calmette–Guerin vaccination or exposure to most nontuberculous mycobacteria (exceptions include *M. kansasii*, *M. marinum*, and *M. szulgai*) [12]. Clinicians should also remember that a negative Mtb screening test does not exclude infection, and positive results in low-prevalence settings are more likely to be false-positive than in higher-prevalence settings.

While episodes of fever are commonplace with undiagnosed primary HIV infection, they rarely last longer than 3 weeks and infection often eludes diagnosis because the illness is subclinical or nonspecific, mimicking a routine flu-like picture [32, 37, 38]. And although the true prevalence of individuals with undiagnosed HIV in this population has not been fully established, some studies have reported the range of FUO-associated primary HIV among those who have been tested is 1.4–5.3% [9, 38]. Given the timely diagnosis of HIV is also a public health priority and that screening and testing for individuals with epidemiological risk factors for acquisition and indicator conditions, regardless of any demographic or behavioral risk assessment, is important to the goal of eliminating HIV transmission, we would agree that screening also represents an important FUO minimal component investigation [39, 40]. Finally, for a FUO patient who is newly diagnosed with HIV-associated acquired immunodeficiency syndrome (AIDS), the fever may likely be caused by an underlying opportunistic infection or malignancy.

Despite the use of specific minimal laboratory and culture investigations as FUO criteria, results of additional post-diagnostic laboratory testing, including cultures and serology, in several studies have yielded a diagnosis in approximately one-fourth of cases [9, 11, 28, 29, 41]. For example, 2 recent meta-analyses of 85 prospective and retrospective studies published between 1997 and 2021, with 19 390 total cases reported, the most useful tests have been serology for microbial pathogens (eg, Cytomegalovirus, Epstein–Barr virus, *Leishmania*, and *Yersinia* species) [9] and autoimmune disorders (eg, systemic lupus erythematosus) [11]. Examination of blood smears has occasionally been diagnostic in some case series, detecting malaria, tick-borne, and/or louse-borne relapsing fevers [9].

A practical point for clinicians is to evaluate the presence of potential diagnostic clues (PDCs) prior to the use of additional laboratory studies (Table 2) [5, 6, 18, 19, 30, 32]. Potential diagnostic clues represent the harnessing of possibly useful aspects of the history, physical examination, laboratory studies, and/or imaging tests to direct next steps. For example, an enlarged axillary lymph node leading to a biopsy helps focus what can be an extraordinarily broad differential diagnosis [5, 6, 18, 19, 30, 32]. Expectations need tempering as an individual PDC may only yield a diagnosis in approximately 20% [32]. Studies have varied on PDC payoffs ranging as high as 62% from a prospective study by De Kleijn and colleagues [18, 19] of 167 patients meeting classic FUO criteria, while Bleeker-Rovers and colleagues [29] reported that an average of 15 PDCs were noted per patient, only 19% of which contributed to the diagnosis. A sobering 81% of PDCs were misleading in this series, a percentage substantially higher than that reported by De Kleijn and colleagues [18, 19], of which 48% of PDCs were misleading. Even though following such clues may lead to dead ends, it is still the most crucial strategy for determining the source of FUO.

#### Molecular Diagnostics

Modern culture systems have become proficient at recovering certain fastidious bacteria (eg, *Brucella* species, HACEK organisms) which often provide the diagnosis promptly before the 3-week time period required to fulfill FUO criteria [9]. Thus, likely due to the relative rarity of such pathogens among FUO series, the advent of enhanced microbiologic culture

**Table 2. Examples of Potential Diagnostic Clues Associated With Selective Causes of Fever of Unknown Origin** [5, 6, 18, 19, 30, 32]

| Category | Cause | Historical Clues | Physical Clues | Laboratory/Imaging Clues |
|---|---|---|---|---|
| INF | Babesiosis (*Babesia microti*, *B. divergens*, *B. venatorum*) | Transmitted by the bite of an *Ixodes* tick in association with outdoor activity (*Babesia microti* in the Northeastern, Southeastern, and upper Midwestern United States, *B. divergens* in Europe, *B. venatorum* in Northeastern China) that may present with symptoms of arthralgias and myalgias. | Relative bradycardia and hepatosplenomegaly. | Anemia (hemolytic), thrombocytopenia, and/or elevated liver enzymes (usually a hepatocellular injury pattern). |
| INF | Bartonellosis (*Bartonella bacilliformis*, *B. quintana*, and *B. henselae*) | Associated with recent travel or residence to the Andes mountains with fever and bacteremia (Oroya fever; *Bartonella bacilliformis*), association with homelessness in urban settings (*B. quintana,* trench fever or endocarditis), or contact with either fleas or the scratch of an infected kitten or feral cat (*B. henselae*, cat scratch disease or endocarditis) and may present with constitutional symptoms of retroorbital pain and anterior tibial bone. | Macular rash, nodular plaque lesions, and/or regional lymphadenopathy. | Largely nonspecific but may reveal anemia, particularly direct invasive hemolytic anemia in the case of *Bartonella bacilliformis*, and autoimmune hemolytic anemia in the case of *B. henselae*. |
| INF | Blastomycosis (*Blastomyces dermatitidis*) | Transmission occurs through contact with soil adjacent to the Mississippi and Ohio River valleys, Saint Lawrence River in New York, Vermont and Canada, and North American Great Lakes, or exposure to infected dogs with patients that may present with symptoms of arthralgias, pelvic pain due to prostatitis, shortness of breath, and cough due to atypical pneumonia and pulmonary nodules. | Verrucous, nodular, or ulcerative skin lesions, especially on the face. | Pneumonia with reticulonodular and miliary radiographic patterns and solitary nodules seen less often than alveolar and mass-like infiltrates as well as mass lesions that mimic malignancy. Hypercalcemia with suppressed parathyroid hormone (PTH) levels may be a clue to the diagnosis that is due to the granulomatous tissue of the infection producing an excess of calcitriol (1,25−dihydroxyvitaminD). Elevated alkaline phosphatase levels (usually >2100 U/L) may also be a clue to disseminated disease, particularly with liver involvement. |
| INF | Blood culture-negative endocarditis | An inflammatory condition of the endocardium with no definitive microbiological etiology following incubation of at least 3 blood cultures with negative cultures after 5 d of incubation in a standard blood culture system that can be due to sterilization from previous antimicrobial therapy, fastidious microorganisms (eg, HACEK, *Legionella* species, nutritionally variant *Streptococci*, and *Pasteurella* species), organisms that cannot be cultured (eg, *Bartonella* species, *Coxiella burnetii*, and *T. whipplei*), or noninfectious causes (eg, Behcet's disease, lupus, and malignancy-associated marantic causes). | Largely nonspecific, but can include chills, fatigue, fevers, night sweats, and weight loss with or without Janeway lesions, Osler nodes, pulmonary emboli, Roth spots, splinter hemorrhages, and/or stroke. | Largely nonspecific, but may include anemia, elevated CRP and ESR, and/or glomerulonephritis. Serological testing should be performed for *Bartonella* species, *Brucella* species, and *Coxiella burnetii*. Polymerase chain reaction methods should be considered for *Bartonella* species, *Brucella* species, *Coxiella burnetii*, *Legionella* species, *Mycoplasma* species, and *T whipplei*, from blood or valve tissue. |
| INF | Brucellosis (*Brucella melitensis*, *B. abortus*, *B. suis*, or *B. canis*) | Associated with recent travel or residence to the Mediterranean basin, Middle East, Asia, Africa, Mexico, and Central and South America with transmission occurring after consumption, inhalation of, or contact with infected animal products (eg, sheep, goats, cattle, camels, or dogs) and possible symptoms of malaise, night sweats, back or pelvic pain. The classic triad is "mold or wet hay" perspiration, migratory arthralgia, and undulant (waxing and waning) fevers associated with chills and sweats. | Camel-back fevers (2-fever peaks per week), fevers tend to peak in the afternoon or early evening, hepatosplenomegaly, hepatomegaly without splenomegaly, suppurative musculoskeletal lesions, spinal tenderness, sacroiliitis, spondylitis, and/or uveitis. Epididymitis/orchitis/epididymal nodule may also be found on evaluation. | Largely nonspecific but may reveal hepatitis and/or pancytopenia. Hypercalcemia with suppressed parathyroid hormone (PTH) levels may be a clue to the diagnosis that is due to the granulomatous tissue of the infection producing an excess of calcitriol (1,25−dihydroxyvitaminD). |

**Table 2. Continued**

| Category | Cause | Historical Clues | Physical Clues | Laboratory/Imaging Clues |
|---|---|---|---|---|
| INF | Coccidioidomycosis (*Coccidioides immitis* or *C posadasii*) | Associated with recent travel or residence to the arid Southwestern United States, northern portions of Mexico, and scattered areas in Central America and South America with transmission occurring by exposure to soil or inhalation of dust and possible symptoms of arthralgias, variable constitutional symptoms. | Pneumonia, erythema multiforme, and/or erythema nodosum. | Pneumonia, pulmonary cavities, and/or pulmonary nodules. |
| INF | Enteric fever (*Salmonella enterica* serovar Typhi) | Associated with recent travel or residence to a low- or middle-income country with consumption of potentially contaminated food or water and possible symptoms of fever, headache, arthralgias, myalgias, abdominal pain, severe diarrhea, and rash. | Usually a sustained high fever 103–104°F (39°C–40°C), may be associated with fever spikes in the morning, relative bradycardia, hepatomegaly without splenomegaly, hepatosplenomegaly, and/or spinal tenderness. A maculopapular rash may be present in the 2nd or 3rd week of illness on the trunk that blanch (fade when pressed), known as rose spots due to the pink color. | Largely nonspecific but may reveal leukopenia and mild hepatitis. |
| INF | Histoplasmosis (*Histoplasma capsulatum*, *H. dubuosii*, and *H. farciminosum*) | Exposure to bat or blackbird excreta in roosts, chicken houses, or caves in the region surrounding the Ohio and Mississippi River valleys of the United States, regions of Central and South America and Australia (*Histoplasma capsulatum*), Africa, and Asia (*H. dubuosii* and *H. farciminosum*) with patients potentially reporting variable constitutional symptoms, nonproductive cough, and headache. | Pneumonia, mucosal and oral ulcers, generalized adenopathy, splenomegaly, erythema nodosum, and/or erythema multiforme. | Pulmonary cavities and/or nodules. Hepatitis, anemia, leukopenia, and/or thrombocytopenia. Hypercalcemia with suppressed parathyroid hormone (PTH) levels may be a clue to the diagnosis that is due to the granulomatous tissue of the infection producing an excess of calcitriol (1,25−dihydroxyvitaminD). Elevated alkaline phosphatase levels (usually >2100 U/L) may be a clue to disseminated disease, particularly with liver involvement. |
| INF | Leishmaniasis (*Leishmania donovani* and *L. infantum*) | Visceral disease, also known as kala-azar or "black fever," is associated with recent travel or residence to areas endemic for transmission by female sandflies and caused by *Leishmania donovani* in Asia and in Eastern Africa, where the pathogens' reservoir is represented by humans, and by *Leishmania infantum* in Latin America and in the Mediterranean area, where a dog is the main reservoir. Needle sharing by people who inject drugs (PWID) has been reported for *Leishmania* transmission. General symptoms may include fevers, night sweats, or weight loss. | Double quotidian fevers (twice daily fever spikes), grayish hyperpigmentation of the face, hand, foot, and/or abdominal skin (referred to as kala-azar occurring more often in South Asia regions) as well as hepatosplenomegaly, hepatomegaly without splenomegaly, and/or generalized adenopathy (East Africa). | Largely nonspecific but may reveal pancytopenia. |
| INF | Leptospirosis (*Leptospira interrogans*) | Transmission occurs variably worldwide after exposure to water or soil contaminated with animal urine, such as rodents, cattle, or horses. Acute phase infection (1–2 wks after infection) is characterized by abrupt high fevers, retro-orbital or bifrontal headaches, myalgia (particularly calves), pre-tibial rash, and red eye. Immune phase (1–4 wks after infection) may include symptoms of headache and neck stiffness, shortness of breath and hemoptysis. | Camel-back fevers (2-fever peaks per week) and relative bradycardia. Acute phase signs may include conjunctival suffusion, jaundice, and pretibial rash. Immune phase signs may include neck stiffness due to aseptic meningitis, hypoxia due to ARDS, and/or hemoptysis due to pulmonary hemorrhage. | Hepatitis with markedly elevated total bilirubin, aseptic meningitis, renal failure (Weil disease), and/or sepsis with ARDS. |

**Table 2. Continued**

| Category | Cause | Historical Clues | Physical Clues | Laboratory/Imaging Clues |
|---|---|---|---|---|
| INF | Q fever (*Coxiella burnetii*) | Associated with farm, veterinary, or abattoir work, consumption of unpasteurized milk, and contact with aerosolized excreta from or contact with infected dairy cows, sheep, goats, and rarely with cats or dogs. Acute disease classically a self-limited illness with abrupt high fevers, retroorbital headache, and shortness of breath. Chronic disease is usually protean with low-grade fevers. | Chronic disease can present with peripheral manifestations of endocarditis, signs of decompensated heart failure, digital clubbing, and purpuric rash on the extremities, or complications of an infected aneurysm or vascular prosthesis (eg, back pain in vertebral osteomyelitis and intraabdominal or gastrointestinal bleeding such as aorto-enteric fistula). | Pneumonia with round opacities on imaging, hepatitis with predominantly elevated AST and ALT, thrombocytopenia (100 000–150 000), elevated autoantibodies, negative blood cultures (generally small vegetations that can be missed on TTE), microscopic hematuria (immune-complex glomerulonephropathy), and elevated inflammatory markers, particularly ESR >50 mm/h. However, in chronic Q-fever inflammatory markers may be completely normal. |
| INF | Whipple disease (*Tropheryma whipplei*) | Migratory arthralgia/arthritis (particularly of ankles, knee, wrist), post-prandial abdominal pain/cramps, chronic diarrhea with weight loss, fatigue, and hyperpigmentation of sun-exposed areas or scars. | Predominantly morning temperature spikes, endocarditis, weight loss, localized lymphadenopathy, hyperpigmentation of sun-exposed areas or scars, malabsorption (particularly due vitamin B12 and D deficiencies resulting in increased melanin synthesis), and malnutrition. | Largely nonspecific but may reveal anemia (particularly microcytic anemia due to iron deficiency and chronic intestinal inflammation with blood loss) and low albumin with negative RF. Stool PCR is a valuable, non-invasive tool, offering high sensitivity and specificity, especially in screening suspected cases. Mesenteric adenopathy and/or cardiac vegetations may be important clues found in imaging studies. |
| NIID | Autoinflammatory diseases presenting with recurrent fevers among adults | Diseases defined as abnormal activation of innate immunity in the absence of infection, do not fulfill a set of diagnostic criteria for a specific autoimmune condition, or respond to conventional immunosuppression with recurrent fevers as a main characteristic. Most of these diseases have an early onset from birth to the first decade of life due to the genetic disorder but diagnoses are often delayed until adulthood. Examples include<br><br>1. *CAPS*, febrile attacks occur over 1–3 d and can be complicated by AA amyloidosis.<br>2. *DADA2*, adult-onset cases are sporadic.<br>3. *HIDS/MKD*, febrile attacks occur every 1–2 m lasting about 1 wk in duration.<br>4. *TRAPS*, febrile flares usually last longer than FMF ranging from 1 to 3 wks and can also be complicated by AA amyloidosis.<br>5. *VEXAS*, usually sporadic cases in males over age 45 y. | Physical clues by condition:<br><br>1. *CAPS*, associated with Muckle–Wells syndrome characterized by cold-induced urticaria, sensorineural deafness, ocular inflammation, headache, and arthritis.<br>2. *DADA2*, most adult-onset cases are associated with vasculopathy mimicking polyarteritis nodosa, livedo racemosa, and ischemic strokes being the main manifestations. A humoral immunodeficiency ranging from isolated Ig class deficiency to pan-hypogammaglobulinemia with recurrent infections may also occur.<br>3. *HIDS/MKD*, associated clinical manifestations include painful cervical adenopathy (>90% of cases), hepatosplenomegaly, urticarial lesions, oral ulcers, abdominal pain with vomiting and diarrhea, and arthritis.<br>4. *TRAPS*, the most prominent manifestation is abdominal pain mimicking an acute surgical abdomen with other manifestations to include erythematous skin lesions of the upper and lower extremities mimicking cellulitis, and migratory myalgias.<br>5. *VEXAS*, usually associated with neutrophilic dermatosis, pulmonary infiltrate, chondritis, and vasculitis. | Laboratory clues by condition:<br><br>1. *CAPS*, associated with *NLRP3* mutations.<br>2. *DADA2*, laboratory diagnosis relies on genetic testing for loss of-function variants of *ADA2*, which encodes adenosine deaminase 2.<br>3. *HIDS/MKD*, an elevated urinary mevalonic acid level during an inflammatory attack may point to the diagnosis as well as MVK gene mutations. An elevated serum IgD level is not specific for MKD.<br>4. *TRAPS*, associated with mutations of the TNF receptor super family protein type 1A encoded by the *TNFRSF1A* gene.<br>5. *VEXAS*, cytopenias (including macrocytic anemia) with vacuoles in myeloid and erythroid progenitors on direct examination, thrombosis, and somatic mutations in the UBA1 gene (found on the X chromosome). |

**Table 2. Continued**

| Category | Cause | Historical Clues | Physical Clues | Laboratory/Imaging Clues |
|---|---|---|---|---|
| NIID | Familial Mediterranean fever (FMF) | A noninfectious genetic disorder caused by a mutation in the *MEFV* gene (codes for the pyrin protein which regulates inflammation) that most often occurs in individuals of Mediterranean or Middle Eastern descent. Characterized by episodes of high fevers typically accompanied by pain in the abdomen (can mimic appendicitis), joints (usually one joint such as the ankle or knee), or chest lasting between 12 and 72 h. Inflammatory (AA) amyloidosis is the main chronic complication and the leading cause of mortality. | Swollen ankle or knee joint. A red rash on the lower extremities (erysipelas-like) affects one-third or less patients. Additionally, abdominal pain and signs of peritonitis as well as chest pain with signs of pleural effusion and pleural inflammation. | During attacks, findings usually show neutrophilic leukocytosis with elevated acute phase reactants such as CRP, ESR, fibrinogen, and serum amyloid A (SAA). Associated with mutations affecting the *MEFV* gene (MEditerranean FeVer). |
| NIID | Giant cell arteritis (GCA) | The most prevalent granulomatous subtype of vasculitis in adults between ages 50 and 70, involving large- and medium-sized arteries, both cranial and extra-cranial, with the highest incidence observed among Northern European and Scandinavian populations. Females are affected more than males. Characterized by episodes of high fevers, typically accompanied by temporal headache, double vision, limb claudication, and jaw claudication. A recent or previous diagnosis of polymyalgia rheumatica should upgrade the level of suspicion. | Physical findings may include lower BMI due to IL-6 production and lipid catabolism, temporal artery thickening, loss of temporal artery pulse, temporal tenderness, relative afferent pupillary defect, posterior ischemic optic neuropathy, and ocular nerve palsy. | ESR of at least greater than 60 but particularly 100 mm/h or more with a platelet count of greater than $400 \times 10^3/\mu L$.<br>Color Doppler ultrasound (CDUS) allows inspection of the complete course of each temporal artery should be performed as soon as possible by an experienced examiner using a machine equipped with a high-frequency linear or hockey stick probe (15 MHz or more) to identify intima-media thickness of the artery or the "halo" sign, which is a hypoechoic halo around the lumen of the temporal artery.<br>High-resolution MR angiogram can be utilized as an alternative for CDUS of temporal arteries and is considered more sensitive than CT angiogram or $^{18}$FDG-PET/CT. However, this may be the population that mostly benefits from $^{18}$FDG-PET/CT as it is the modality of choice for ruling out malignancies that are not unusual in GCA patients (eg, cutaneous cancers, colonic adenocarcinoma, prostate adenocarcinoma, and myeloid malignancies, but lower risk of breast cancer). |
| NIID | Kikuchi disease (also known as Kikuchi–Fujimoto disease or Kikuchi histiocytic necrotizing lymphadenitis) | A benign, self-limited illness characterized by subacute (usually over 2–3 wks) swollen and painful lymph nodes, often in the neck (cervical lymphadenopathy), usually accompanied by mild fever and night sweats. Other symptoms can include fatigue, body aches, and a rash. | Swollen lymph nodes that involve mainly the posterior cervical triangle. An erythematous (red) rash, often appearing as macules, papules, or plaques on the face, trunk, and upper extremities, may be observed in 30–40% of cases. Other skin manifestations can include lupus-like lesions, leukocytoclastic vasculitis, oral ulcers, and alopecia. | Largely nonspecific, but Leukopenia can be found in up to 50% of the cases. Atypical lymphocytes in the peripheral blood have been observed. |

**Table 2. Continued**

| Category | Cause | Historical Clues | Physical Clues | Laboratory/Imaging Clues |
|---|---|---|---|---|
| NIID | Polyarteritis nodosa | A systemic vasculitis of adolescents and adults affecting small or medium-sized muscular arteries that typically involves the renal and visceral vessels but spares the pulmonary circulation. The classic presentation is associated with rapidly accelerating hypertension, abdominal pain and bloody stools caused by vascular gastrointestinal lesions; diffuse muscular aches and pains; and peripheral neuritis, malaise, fever, and weight loss. | Rapidly accelerating hypertension and Roth spots may be observed. Livedo racemosa, nodules, papules, and ulcerations of the skin as well as mononeuritis multiplex. Calf pain can be a distinctive clue. | Largely nonspecific but may reveal renal failure, anemia, and elevated inflammatory markers. There is no association with anti-neutrophil cytoplasmic antibodies (ANCAs). A third of the patients have serologic evidence of chronic hepatitis B virus (HBV) infection, which leads to the formation of immune complexes containing hepatitis B antigens that deposit in affected vessels (ie, type III hypersensitivity). |
| NIID | Polymyalgia rheumatica | Gradual onset (more than 4 wks) of symmetrical morning stiffness of shoulder (70–95%), hip girdle, and neck lasting approximately 45-minutes associated with fevers, malaise, depression, anorexia and weight loss, and sleep disturbances. Distal, transient, asymmetrical arthritis, primarily in the knee or wrist, may also occur. Rapid response to prednisone (less than 20 mg/day). This condition can be associated with giant cell arteritis. | Proximal muscle weakness of the shoulders and hips, as well as decreased range of motion and occasional temporal artery region tenderness (due to a subset of patients also presenting with giant cell arteritis). Tenosynovitis of the biceps tendon. Arthritis of the wrist can cause carpal tunnel syndrome. | Anemia and ESR greater than 40 mm/h with exclusion of other rheumatological/ musculoskeletal diseases. An ESR greater than 100 mm per hour should raise concern for concomitant giant cell arteritis or underlying malignancy (eg, paraneoplastic syndrome). Tenosynovitis of the biceps tendon and bursitis of the subdeltoid bursa are characteristic finds on musculoskeletal ultrasound. |
| NIID | Sarcoidosis | A multisystemic granulomatous disease of unknown etiology with a predilection for nonsmoker adults younger than age 40 y that present with dry cough with shortness of breath, dry eyes with photophobia, facial palsy, parotid gland swelling, indurated purple skin plaques, erythema nodosa, arthralgia/arthritis (particularly the ankles), and/or erythema nodosa. | Peripheral lymphadenopathy, erythema nodosum, periarthritis of the ankles, arthralgias, eye involvement with iritis or iridocyclitis, suppression of lacrimation with parotid gland swelling, lacrimal gland enlargement, facial palsy, splenomegaly, or hepatomegaly, and epididymitis/orchitis/epididymal nodule may also be found on evaluation. Lupus pernio is a rare specific manifestation of sarcoidosis that more common among women, characterized by red-to-purple, firm nodules and plaques, most commonly on the nose, ears, and cheeks. | Mediastinal and hilar lymphadenopathy on chest imaging with the incidental finding of noncaseating granulomas; and laboratory clues might include elevated serum and urinary levels of calcium (most common electrolyte abnormality), and angiotensin-converting levels. Serum soluble interleukin-2 receptor (sIL-2R) is a recognized, sensitive biomarker for sarcoidosis, showing high sensitivity (~88%) and specificity (~85%). |
| NIID | Schnitzler syndrome | A rare acquired autoinflammatory disorder with average age of onset of 50–55 y with a slight male Caucasian predominance. The syndrome is characterized by a chronic urticarial rash associated with immunoglobulin M (IgM) monoclonal gammopathy, recurrent fevers without chills, arthralgias, and bone pain (most commonly affecting the lower limbs such as the tibia, femur, or pelvis). | A recurrent neutrophilic urticarial rash is the first presenting symptom, which may precede others by months or even years, located on the limbs and trunk, often sparing the face, palms, and soles. Axillary and/ or inguinal adenopathy may be present in 25% of cases. | The syndrome is mainly associated with monoclonal IgM gammopathy with a kappa light chain (85% of cases). C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) is almost always elevated. A complete blood count often reveals neutrophilic leukocytosis. Thrombocytosis and anemia may be present due to chronic inflammation. Alkaline phosphatase levels may be elevated due to abnormal bone remodeling. |
| NIID | Still disease, adult-onset | 2-wk arthralgia/arthritis, 1-wk high-grade fever ≥39.0°C (102.2°F), and sore throat. While rare this condition can trigger either hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) and can occur in patients with other rheumatic diseases such as primary Sjögren syndrome (SS). | Hepatosplenomegaly, hepatomegaly without splenomegaly, generalized or localized lymphadenopathy (particularly cervical), polyarthralgia and arthritis, pharyngitis, and transient, salmon-colored rash with fever spikes. | Marked hyperferritinemia (often >2000 ng/mL), neutrophilic leukocytosis (>80.0%), anemia, thrombocytosis, transaminitis (without hyperbilirubinemia), and/or coagulopathy with negative RF and ANA. |

**Table 2. Continued**

| Category | Cause | Historical Clues | Physical Clues | Laboratory/Imaging Clues |
|---|---|---|---|---|
| NIID | Subacute painful thyroiditis (also known as De Quervain thyroiditis, granulomatous thyroiditis, or giant cell thyroiditis) | A self-limited inflammatory condition of the thyroid gland that more commonly affects females between ages 25 and 35, usually in association with a recent viral infection (eg, coxsackieviruses, influenza, measles, mumps, and SARS-CoV-2) 2–8 wks prior to onset of symptoms, lasting weeks-to-months and characterized by a triphasic clinical course; an initial transient thyrotoxicosis followed by hypothyroidism, and then return to normal thyroid function in over 90% of cases. | Fevers, myalgia, malaise, and tender, firm, enlarged thyroid gland in the thyrotoxicosis phase. | High serum thyroglobulin levels (T3 and T4), elevated ESR and CRP levels, anemia, leukocytosis, and low radioiodine uptake in the thyrotoxicosis phase. Thyroid-stimulating hormone (TSH) levels are elevated with low T4 levels during the hypothyroid phase. |
| NIID | Systemic lupus erythematosus[a] | A multisystem disorder that predominantly affects women of reproductive age systemic that may present with a wide variety of signs and symptoms often involving multiple organ systems. In FUO, fevers tend to be daily, single fever spikes but less commonly may be intermittent and are not accompanied by chills (an important feature in differentiating bacterial infections). | Patients often have a skin rash (eg, malar or discoid), photosensitivity, oral ulcers, palpable purpura, livedo reticularis, arthritis, serositis (eg, pericarditis, pleuritis), and Raynaud phenomenon as a more common initial manifestation. Lacrimal gland enlargement, Roth spots, and epididymitis/orchitis/epididymal nodule may also be found on evaluation. | Largely nonspecific but may reveal hepatitis, renal failure, anemia, and elevated inflammatory markers (eg, CRP and ESR). ANA-positive homogenous pattern with anti-dsDNA antibodies in highly specific (95%) that can fluctuate with disease activity. Other findings may include hypocomplementemia with low C4, C3, and CH50. |
| ONC | Hodgkin lymphoma | A B-cell–derived lymphoma associated with malignant Reed–Sternberg cells that has a bimodal age distribution (peaks at 15–35 and 50–70 y) associated with 4 subgroups (nodular sclerosis, mixed cellularity, lymphocyte rich, and deplete). The nodular sclerosis and mixed cellularity types are thought to be facilitated by prior EBV and human immunodeficiency virus (HIV) infections. | Adenopathy (cervical >, axillary, mediastinal, and para-aortic). | Largely nonspecific but can include elevated CRP. Eosinophilia may be found in up to 20% of cases. |

This table was adapted and modified from Wright WF, Durso SC, Forry C, Rovers CP. Fever of unknown origin. *BMJ*. 2025;388: e080847.

Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibodies; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CAPS, cryopyrin-associated periodic syndrome; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; HACEK, refers to genera of *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*; HIDS/MKD, hyper-Ig D syndrome/mevalonate kinase deficiency; INF, infectious disease; MEFV, Mediterranean fever gene; NIID, noninfectious inflammatory disorder; ONC, oncologic disorder; PCR, polymerase chain reaction; RF, rheumatoid factor; TRAPS, TNF receptor–associated periodic syndrome; TTE, transthoracic echocardiogram; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.

[a]The ESR/CRP ratio may be useful to differentiate between infection and flare in SLE patients, where a ratio above 15 was significantly correlated with disease activity and a ratio below 2 was associated with infection ($P = .000$) (reference: Littlejohn E, Marder W, Lewis E, et al. The ratio of erythrocyte sedimentation rate to C-reactive protein is useful in distinguishing infection from flare in systemic lupus erythematosus patients presenting with fever. *Lupus* 2018;27:1123–9).

systems has paradoxically had less impact on the proportion of successful diagnoses than anticipated [9]. Molecular diagnostic techniques, therefore, may overcome these and other drawbacks to modern conventional culture-based testing such as reduced sensitivity with empirical antibiotic use and inability to culture fastidious microorganisms in commercial systems (eg, *Bartonella* species, *Tropheryma whipplei*) [12, 30, 42, 43]. One of these techniques, next-generation sequencing, entails the objective sequencing of genetic material in a specimen [42]. Other approaches include broad-range or pathogen-specific PCR assays that target the 16S or 18S ribosomal RNA gene for bacteria, D1-D2 region of ribosomal DNA, internal transcribed spacer, and other regions of bacterial and fungal genomes [42].

One recent systematic review involving 8 studies published from 2000 to 2020 reported 13 of 24 (54.2%) molecular assays helped reach a final infection diagnosis [42]. While not a genuine FUO study, a recent single-center 2-year retrospective study with 149 febrile patients analyzed within 3-days from admission with metagenomic next-generation sequencing methods on samples of blood, bone marrow, bronchoalveolar lavage fluid, sputum, or secretions detected 190 pathogens (including fastidious/nonculturable pathogens such as *Brucella melitensis*, *Leishmania donovani*, and Mtb) compared to 73 detected by traditional microbiology methods [43]. These methods are not yet first-line testing and should be reserved for patients who remain with unexplained fevers due to suspected infections despite a specialist evaluation, given our limited knowledge base and barriers to this expensive technology [12]. Notable barriers to this technology, particularly next-generation sequencing, include availability, high cost, consideration of sequencing depth, need for nonculture-based validation methods, and difficulty distinguishing pathogenic from colonizing microorganisms (ie, high sensitivity with potential for low specificity) [42–44].

#### Imaging

The advancement of imaging and biomarker analysis techniques, such as computed tomography (CT), magnetic resonance imaging (MRI) with either whole body or diffusion-weighted protocols, and $^{18}$F-fluorodeoxyglucose–positron emission tomography ($^{18}$FDG-PET/CT), provides opportunities to identify focal inflammatory or infectious processes, particularly when CT scans alone are not rewarding [20, 44–48]. Computed tomography of the abdomen and, to a lesser extent, ultrasound imaging of the gallbladder and hepatobiliary system have been used extensively to evaluate cases [18, 19, 29]. However, false-negative CT studies have occasionally been encountered, or are expected, in cases of abscesses, giant cell arteritis, or infiltrating malignancies in solid organs because of distortions of normal anatomy, small lesion size, or failure to use both oral and intravenous contrast agents [29]. Among the commonly employed diagnostic imaging methods, a multicenter prospective study [29] involving 73 patients reported diagnostic sensitivity of 60% for plain-film chest radiography, 82% for chest CT, 86% for abdominal ultrasound, and 92% for abdominal CT. Transthoracic echocardiography in 2 prospective studies [18, 19, 29] involving 457 patients found it useful in only 13 of 258 (5.0%) tests but should be pursued with cardiac disease PDCs (eg, suspected pericarditis or heart valve abnormality).

Whole-body MRI had a diagnostic yield of 71% and changed management in nearly 50% of cases compared with conventional imaging tests [46]. Furthermore, application of diffusion-weighted MRI is beneficial for evaluating the central nervous system and within the abdomen, the spleen, and lymph nodes [49]. In a series of 67 patients undergoing FUO evaluation, Wagner and colleagues [49] reported that the application of MRI to the aortic arch and proximal cervical arteries in selected patients improved the diagnosis of large vessel vasculitis by 20%. The most common diseases diagnosed by this testing modality were giant cell arteritis (55%), Takayasu arteritis (27%), granulomatosis with polyangiitis (9%), and microscopic polyangiitis (9%). In another series involving 119 consecutive patients with CRP levels over 5 mg/L, other signs of inflammation (ie, fatigue, muscle pain, arthralgia, and night sweats), and/or more than 3 weeks of fever ≥38.3°C [100.9°F] on >3 occasions, $^{18}$FDG-PET with MRI offered a reliable radiation-reduced option for diagnosing suspected noninfectious inflammatory conditions such as Adult-onset Still disease or large vessel vasculitis with or without signs of polymyalgia rheumatica [50]. However, until further data becomes available, MRI combined with $^{18}$FDG-PET is considered exploratory for FUO patients.

The first guideline with criteria for the use of nuclear medicine for adult FUO was recently published [30, 47]. Pooled data from this guideline and several other meta-analyses [20, 30] demonstrate diagnostic yields of 84.0–98.0% for $^{18}$FDG-PET/CT. $^{18}$FDG-PET/CT enabled detection and localization of hypermetabolic lesions with high sensitivity because of $^{18}$F-FDG uptake in glycolytically active cells may represent inflammation, infection, or neoplasia [20, 30, 44–48]. Notably, patients with either infection or malignancy benefited more from $^{18}$FDG-PET/CT than those with noninfectious inflammatory disorders [30, 47]. One exception is that $^{18}$FDG-PET/CT is very useful for detecting mural inflammation or luminal changes of intracranial and extracranial arteries in patients with giant cell arteritis, a large vessel vasculitis commonly associated with polymyalgia rheumatica [11, 30, 51]. Additionally, a negative $^{18}$FDG-PET/CT result has correlated with spontaneous remission of fevers that were approximately 6 times higher (RR = 5.6; 95% CI: 3.4–9.2; $P < .001$) than patients with positive results [30, 52]. These findings suggest that $^{18}$FDG-PET/CT imaging could be performed earlier in the evaluation process (ie, after a patient fulfills FUO defining criteria) and also could provide prognostic information if negative, particularly when other less costly investigations have been exhausted and when scans are

used among patients with unintentional weight loss of at least 5.0% over the previous 6 months and anemia (eg, hemoglobin <10.7 g/L) [20, 47].

Two recent publications report significant diagnostic contributions of $^{18}$FDG-PET/CT, particularly compared to chest-abdomen-pelvis CT that may represent a cost-effective strategy in both defining and evaluating FUO patients [53, 54]. However, there are no rigorous studies directly comparing $^{18}$FDG-PET/CT to the currently recommended minimal imaging investigations that define FUO patients [12, 35]. Therefore, until further data becomes available, there was strong consensus agreement among Delphi consensus experts [12] to use $^{18}$FDG-PET/CT only after patients fulfill all the criteria of the updated FUO definition. Limited access in some geographical locations and costs of performing scans present significant barriers to using $^{18}$FDG PET-CT compared to plain film, ultrasound, or conventional CT [36].

#### Invasive Procedures and Biopsies

In most published series, histopathologic examination of tissues obtained by invasive procedures gave the final answer in fewer than half of cases. Still, it should be considered when the cause of fever remains unidentified in the presence of a PDC (eg, lymph node or pleural biopsy in a suspected case of tuberculosis with pleural effusion) [4, 32, 55, 56]. An average of 2 or 3, sometimes even more, separate biopsies may be required to establish a diagnosis [4]. In a recent retrospective study of 100 patients by Mete and associates [53], invasive procedures were performed in 79% of patients with a diagnostic benefit obtained in 49% of cases. Biopsies were the most common invasive procedure, yielding a diagnosis in 42% of cases. The diagnostic contribution of laparoscopy and laparotomy was most helpful in patients with carcinomatosis, solid cancers not approachable by other means, lymphomas, and disseminated tuberculosis [55, 56].

Bone marrow and liver biopsies are potentially worthwhile alternative techniques for diagnosing prolonged fevers in immunocompetent patients, particularly if there are liver enzyme abnormalities, anemia (ie, hemoglobin <11 g/dL), and/or thrombocytopenia (ie, $<150 \times 10^3/\mu L$) [18, 19, 29, 31, 57]. In the series from de Kleijn and colleagues [18, 19], bone marrow biopsies enabled a diagnosis in 9 (18.4%, n = 49) cases of hematologic malignancies. In the same series, liver biopsy enabled diagnoses in 3 (8.8%, n = 34) cases (ie, adenocarcinoma, disseminated cryptococcosis, and granulomatous hepatitis). Bleeker-Rovers and colleagues [29] reported that bone-marrow biopsies were helpful in 2 (10.5%, n = 19) cases of malignancies, and liver biopsy was helpful in 1 (14.3%, n = 7) case of persistent yersiniosis. In a recent retrospective series of 130 FUO cases by Hot and colleagues [57], bone marrow biopsy enabled a diagnosis in 31 patients (23.8%) with malignant hematological diseases diagnosed in 25 cases (80.6%), infectious diseases in 3 cases (9.6%), systemic mastocytosis in 2 cases (6.5%), and idiopathic disseminated granulomatosis in 1 case (3.3%). Pathological examination of the bone marrow sample was the sole diagnostic tool in 23 observations.

## THERAPEUTIC APPROACH

Although data from several observational studies [5, 29, 58] have illustrated the effectiveness of empirical therapy initiated in expert referral centers for unexplained FUO, a fundamental principle of FUO management is that therapy should be withheld whenever possible until the cause has been determined so treatment can be tailored to a specific diagnosis. Delphi panel experts recommended empiric therapeutic trials (eg, antimicrobials, corticosteroids, and/or anti-inflammatory agents) should be reserved for very few patients in whom all other approaches have failed or those so seriously ill that therapy cannot be withheld for a further period of observation [12]. Important exceptions in which treatment should not be withheld include suspected temporal arteritis to prevent vascular complications such as blindness or stroke, hemodynamically unstable immunocompetent patients, fevers among newly discovered immunocompromised or neutropenic patients, and where tuberculosis is highly prevalent and suspected but cannot be confirmed after performing appropriate tests [30].

## PROGNOSIS AND SPONTANEOUS RESOLUTION

Prognosis is based on the underlying disease or disorder, with the worst prognoses occurring in older individuals and those with malignant neoplasms [4, 16, 18, 19, 21, 29, 32, 58–60]. Diagnostic delay also affects the prognosis adversely, particularly in intra-abdominal infections and miliary tuberculosis [32, 58, 59]. However, and in general, patients who remain undiagnosed after an extensive evaluation tend to have a favorable outcome [4, 16, 32, 58, 59].

In older series, a mortality rate of 12–35% has been reported for FUO-associated diseases [4, 16, 21, 59]. For example, in a series of 91 patients undergoing evaluation, Mansueto and colleagues [4] described 29 patients (31.8%) who were discharged without a diagnosis and followed for 48 months. Although a definitive diagnosis was established in 8 cases, 4 patients (13.7%) died because of noninfectious complications related to previously unrecognized primary neoplastic conditions. In a more recent analysis among 436 immunocompetent adults presenting with FUO between 2000 and 2010, Vanderschueren and colleagues [60] reported a mortality rate of 6.9%. Although malignancy accounted for 11% of FUO cases, it carried a disproportionately higher fatality rate (60%) among patients with non-Hodgkin lymphoma [58]. Fatality rates were <6% among other categories.

Spontaneous resolution, with or without an eventual diagnosis, has been reported in as many as 75% of patients [18, 19, 29, 58]. Bleeker-Rovers and colleagues [29] reported spontaneous resolution in 21 of 37 patients after a median follow-up of 12 months and empirical treatment with nonsteroidal anti-inflammatory agents or corticosteroids. In a recent questionnaire-based cohort study of 131 unexplained FUO patients followed for a median duration of 60 months (range, 0–177 months), spontaneous resolution occurred in 47.3% [58]. Mortality for this cohort was 6.9% and unrelated to febrile diseases.

Efforts have also been made to track outcomes and determine whether referrals for a second opinion to an expert center are delivering higher quality services and improved outcomes [5]. In a retrospective cohort study of 236 FUO patients referred to an expert center, Mulders-Manders and colleagues [5] reported a total positive yield with diagnoses and treatment-initiated resolution of fever in 68.2% of cases evaluated using a standardized diagnostic protocol with early access to specialized diagnostic methods (eg, $^{18}$FDG-PET/CT). Among patients who remained undiagnosed, the authors reported a favorable prognosis. Mortality for this cohort was 2.1% and unrelated to the febrile diseases.

## PATIENT COUNSELING AND FOLLOW-UP CONSIDERATIONS

Patient education and a longitudinal care plan are crucial for evaluating outcomes. Close monitoring of clinical changes is necessary, and patients should be informed about potential adverse effects from empirical treatments. Contingency plans must be in place to manage these effects or switch therapies as needed. Additionally, ongoing management of existing conditions is of utmost importance.

## OTHER SIMILAR SYNDROMES

Fever of unknown origin and inflammation of unknown origin (IUO) are closely related conditions that share similar diagnostic criteria and underlying etiologies [12, 27, 28, 61]. In 2009, Vanderschueren and colleagues [60] defined IUO as a condition lasting longer than 3 weeks without high-grade fevers (ie, temperatures less than 100.9°F [38.3°C]), CRP levels greater than 30 mg/L, and/or ESR greater than age/2 in males (or [age +10]/2 in females) on more than 3 occasions, with no diagnosis despite appropriate investigations after at least 3 outpatient visits or at least 3 days in the hospital. Delphi panel experts recommended the same diagnostic approaches used in FUO can be applied to IUO and that clinicians and researchers use the same standardized set of 5 diagnostic disease categories when classifying associated causes [12].

## CONCLUSION

Diagnosing the underlying cause of FUO is often complex, as patients typically present with atypical symptoms of common diseases rather than rare conditions. Utilizing Delphi-generated consensus FUO criteria can help define the patient population and improve diagnostic processes, facilitating future comparisons in research. Key elements in FUO evaluations include considering geographical disease prevalence and conducting thorough history and physical examinations to identify potential diagnostic clues. $^{18}$FDG-PET/CT aids in localizing inflammation, infection, or neoplasia that are not evident in initial tests. A personalized clinician approach, informed by findings and the patient's therapy tolerance, is essential. Effective management typically requires a coordinated, multidisciplinary strategy to ensure optimal evaluation and accurate diagnosis for targeted treatment.

## Notes

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