Approach of fever of unknown origin in general practice

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Abstract

Fever of unknown origin (FUO) remains a diagnostic challenge in primary care due to its broad differential diagnoses and the absence of a single gold-standard diagnostic test.

This scoping review explores recent literature and proposes a practical diagnostic approach for general practitioners in primary care regarding diagnostics of FUO.

Databases including PubMed and Embase were systematically searched for studies published since 2010.

The results emphasize the importance of structured clinical reasoning beginning with comprehensive history taking, followed by physical examination, basic laboratory testing, and appropriate imaging.

A stepwise, structured algorithm is proposed to streamline diagnostic yield, reduce unnecessary testing, and guide timely referral to the hospital.

This review wishes to add general practice specific focus to the already existing guidelines with integration of recent recommendations regarding FUO.

1 Introduction

1.1 Fever of unknown origin

1.1.1 Definition

Fever of unknown origin (FUO) is a challenging diagnosis, describing a syndrome defined using accepted diagnostic criteria but without a classic, clear-cut gold standard of measurement (1).

The condition was first described in 1930, defined with a standard set of criteria in 1961 by Petersdorf *et al*. as: “A record of oral temperature >38.3°C on at least three different occasions, for a minimum duration of three weeks, in the absence of diagnostic hypotheses that could explain the fever after one week of diagnostic evaluation in hospital.” (2).

The definition was modified to include outpatient health-care contacts and suggested to be divided into four groups (classic, nosocomial, HIV-related, and neutropenic) in 1991 by Durack *et al*. (3).

In 1997 the definition was updated with quantitative measures by De Kleijn *et al*. such as immunocompetent patients and no diagnosis despite bloodwork, urine sediment and culture, chest x-ray and abdominal ultrasound (4).

In 2021, a new definition for FUO in the immunocompetent adult patient was proposed: “More than 3 weeks of fever (≥38.0°C) without explanation, despite completing a set of minimal standard diagnostic tests in an immunocompetent patient.” (5).

In a subsequent review, the authors underlined that although some diagnostic work-up is required, it must not be too rigid and should allow room for subjective evaluation of what “reasonable investigations” and “sufficient time” covers (6).

FUO remains highly prevalent worldwide and can affect all age groups, with some peculiarities at extreme ages and in special groups. Most of the times, it can be divided into 5 different causal categories: infectious, rheumatological (non-infectious inflammatory disorder (NIID)), neoplastic and miscellaneous etiologies. If no etiology is found, it is classified as idiopathic FUO.

With well over 200 possible differential diagnoses, it remains a diagnostic challenge

even for the experienced clinician. A methodological approach with clinical deductive reasoning and value-based investigative work-up can help establish the diagnosis (7, 8).

1.1.2 Epidemiology

Epidemiology of the cause of FUO varies globally and depends on local disease prevalence, healthcare accessibility, diagnostic criteria that are used and patient demographics. Infectious causes remain predominant in low- and middle-income regions, whereas non-infectious inflammatory and neoplastic conditions are more frequent in high-income countries (6, 9, 10).

1.1.3 Pathophysiology

The human body temperature follows a daily pattern where it regulates the body temperature within a certain range (35.6°C-38.2°C: mean 36.8 ± 0.4°C, measured orally). The lowest temperature is measured at 6 a.m. in the morning (37.2°C max. normal) and the highest temperature is measured at 4-6 p.m. (37.7°C max. normal).

The female sex also has slightly higher body temperature depending on the menstrual cycle, with its highest point during the luteal phase (11).

A systematic review by Sund-Levander *et al*. studied the differences in range and in mean body temperature using different methods of measuring when comparing both sexes. They concluded that there was a wider range of normal body temperature, especially for the lower values, and that several other factors such as the place of measurement, sex and age should be taken into consideration. When summarizing these studies, they found that the range for oral temperature was 33.2-38.2 °C, rectal: 34.4-37.8 °C, tympanic: 35.4-37.8 °C and axillary: 35.5-37.0 °C.

They also compared the body temperature measured orally, rectally, axillary and tympanic and found that the temperature was 0.6°C higher when measured centrally (e.g., rectally) vs peripheral (e.g., orally or axillary) (11).

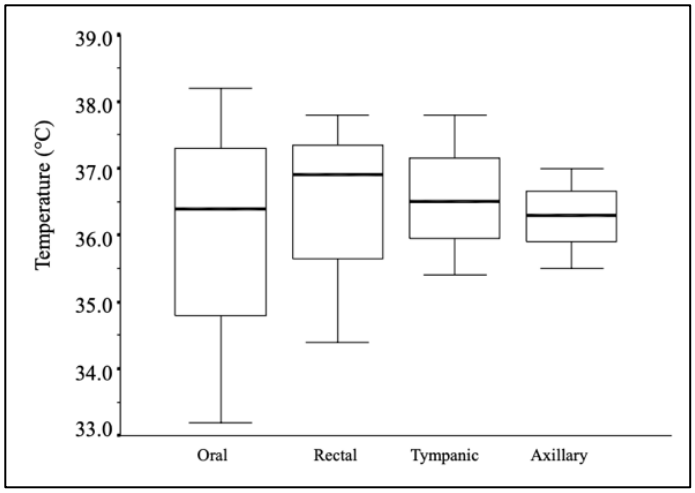


Figure 1. Difference between median temperature measured by different methods. (11)

The study from Wright *et al*. concluded that when fever is documented and reported, researchers and clinicians should clearly specify the cut-off temperature used in determining the presence of fever, the anatomic site at which temperatures are taken, and the instrument used to measure temperatures should be described (6). As such it is easier to make comparisons and conclusions from data as they can more uniformly be compared to one another.

The body temperature also differs throughout history, as a study by Protsiv *et al*. shows. They investigated the average body temperature in the United States of America and made a comparison between before and after the industrial revolution. They determined that the mean body temperature in both men and women, after adjusting for age, height, weight and, in some models date and time of day, has decreased monotonically by 0.03°C per birth decade. They dedicate this to physiologic differences, most likely a decrease in metabolic rate. Although there are many factors that influence resting metabolic rate, change in the population-wide level of inflammation seems the most plausible explanation for the observed decrease in temperature over time. Economic development, improved standards of living and sanitation, decreased chronic infections from war injuries, improved dental hygiene, the waning of tuberculosis and malaria infections, and the dawn of the antibiotic age together are likely to have decreased chronic inflammation since the 19th century (12).

The study by Wright *et al*. from 2024 found that while panelists favored lowering the traditional threshold of 38.3°C (100.9°F) for FUO to 38.0°C (100.4°F), this did not reach a consensus. Reasons for lowering the threshold are that 38.0°C is considered the standard upper level of normal and investigators have reported mean body temperatures in men and women, after adjustment for age, height, and weight, have decreased monotonically by 0.03°C per birth decade since the 1890s as shown in the study by Protsiv *et al.* Therefore, lowering the temperature threshold for FUO might improve sensitivity (6).

This confirms the need for an evolving definition of FUO and the necessity of new studies. For this study, fever as such, will be defined as a body temperature of ≥38.3 °C measured centrally.

The cause of fever can be divided into 2 large categories that both use the same pathways to elevate the body temperature by interacting with the organum vasculosum of the lamina terminalis (OVLT), leading to the production of fever

Firstly, there are the exogenous pyrogens (e.g. micro-organisms). They can either act directly on the OVLT or stimulate cytokine production.

Secondly there are the endogenous pyrogens (e.g. interleukin (IL)-1, IL-6, Tumor necrosis factor (TNF)- α) that can stimulate the OVLT directly. Even in absence of infection these pyrogens can be produced and can cause fever (inflammation, trauma, antigen-antibody complexes).

The stimulation of the OVLT leads to increased synthesis of prostanoids including prostaglandin (PG)E2, which acts in the pre-optic nucleus of the hypothalamus slowing the firing rate of the warm sensitive neurons and resulting in an increase in body temperature, thus creating the fever (13).

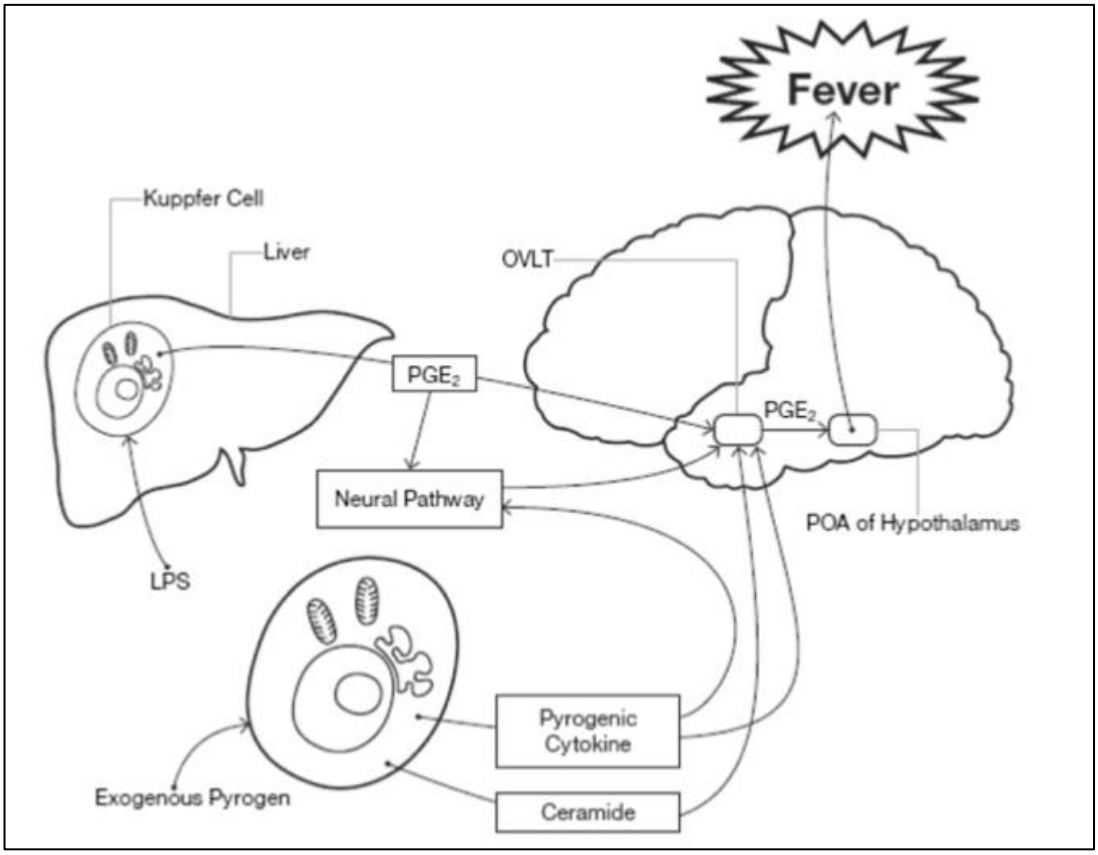


Figure 2. Pathophysiology of fever. (13)

The bioactive lipid derivative, ceramide, which has a proapoptotic as well as a cell signaling role, may act as a second messenger independent of PGE2, and may be of particular importance in the early stages of fever generation. Lipopolysaccharides (LPS) from gram-negative bacteria may stimulate peripheral production of PGE2 from hepatic Kupffer cells. LPS-stimulated fever may also be neurally mediated. Neural pathways may account for the rapid onset of fever, with cytokine production responsible for the maintenance, rather than the initiation, of fever. Fever generation is also thought to occur by signaling via the Toll-like receptor cascade, which may be independent of the cytokine cascade (13).

Note that it is important to differentiate between fever and hyperthermia. With hyperthermia the rise in body temperature is not due to a higher hypothalamic set point as mentioned above, but to excessive heat production or impaired heat dissipation, as in heat stroke or malignant hyperthermia (14, 15).

1.1.4 Aims and objectives

The objective of this study is to review the recent literature on the diagnostic approach of FUO in primary care and to conclude this in a clinical algorithm for daily practice.

In this study we will try to generalize the necessary work-up as a guideline for FUO in primary care starting with the clinical history, physical examination, necessary testing and imaging in the general practice.

2 Methods

2.1 Study criteria

This scoping literature review aims to search the published literature on approach of fever of unknown origin in general practice. The Embase database and Medline database, via the Pubmed interface, were searched for relevant information.
Articles published since 2010 and written in English or Dutch were included.
No specific study types were selected.

2.2 Search methods for identification of studies

2.2.1 Electronic search

To review the published research on the approach of fever of unknown origin in general practice, 2 databases were searched: Medline, via the Pubmed interface, and Embase. These databases were systematically searched using a combination of the keywords “Fever of unknown origin” and “General practice”.

2.2.1.1 Pubmed

(fever of unknown origin[Title/Abstract]) AND (GP[Title/Abstract] OR general practitioner OR family practice OR general practice OR outpatient[Title/Abstract])

Only articles written in English or Dutch and published since 2010 were included. This search resulted in 79 articles.

2.2.1.2 Embase

('fever of unknown origin'/exp OR 'fever of unknown origin') AND (gp OR 'general practitioner'/exp OR 'general practitioner' OR 'family practice'/exp OR 'family practice' OR 'general practice'/exp OR 'general practice')

Only articles written in English or Dutch and published since 2010 were included. This search resulted in 62 results.

2.2.2 Manual search

Manual search concluded in 7 articles

3 Results

3.1 Search results

Both of these searches resulted in a combined number of 132 articles on the 30 March 2025. 79 from Medline (via PubMed interface) and 62 from Embase.

Immediately 3 duplicates were removed as they overlapped between the 2 databases.

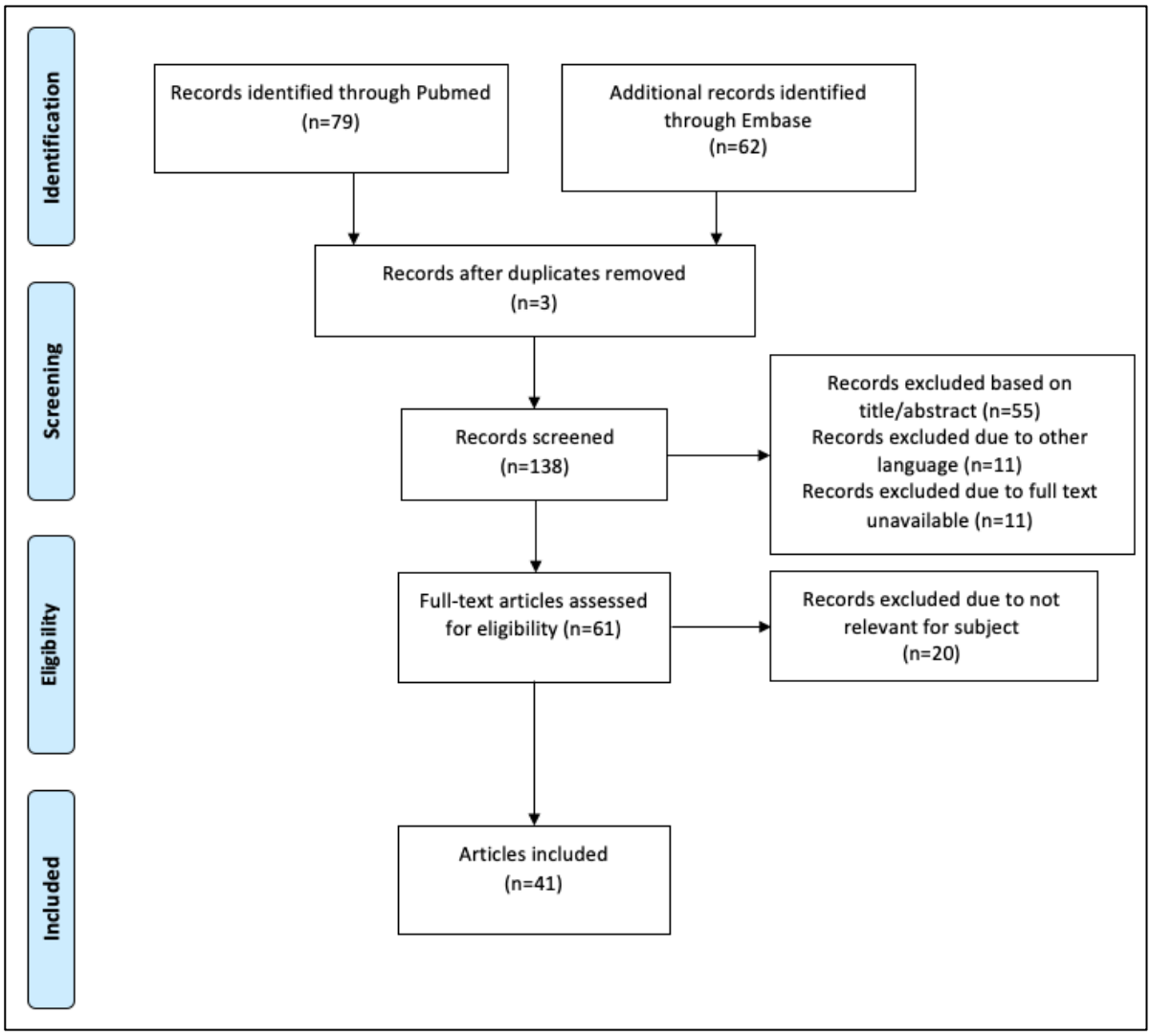


Figure 3. PRISMA flow diagram

The 138 remaining articles were screened on relevance based on their title and abstract and removed if they did not match our research question.

In this way 55 articles were excluded,

Eleven additional articles were excluded based on their language.

Another 11 articles were excluded due to full text being unavailable.

The 61 remaining articles were screened on relevance based on the full text from which 41 were included in the final selection.

3.1.1 Definition

For this article, we will be using the most recent definition for FUO as defined by Wright *et al*.: “More than 3 weeks of fever (≥38.0°C) without explanation, despite completing a set of minimal standard diagnostic tests in an immunocompetent patient.” (5).

3.1.2 Clinical history

A comprehensive history, is one of the key factors in approaching a patient with a complex illness such as FUO and can already provide potential diagnostic clues (PDC) for further investigation. The clinical history can be of important guidance in establishing a diagnosis by determining the choice of the initial laboratory investigations and further necessary testing. As such we can try and avoid unnecessary testing.

All symptoms need to be considered as relevant since most patients with FUO present with a common disease that is atypically manifested (16).

3.1.2.1 Verification of fever and fever patterns

Verification of fever is an essential yet frequently neglected step in the evaluation of FUO. Objective temperature documentation is crucial, as in a series of 347 patients admitted to the National Institutes of Health for investigation of prolonged fever, 35% were ultimately determined not to have significant fever. Therefore, fever should be accurately documented (16).

Clinicians have endeavored to diagnose particular diseases by analyzing the associated fever patterns since the earliest days of clinical thermometry. These efforts have given rise to an extensive and frequently arcane terminology, including descriptors such as *remittent, intermittent, hectic, quotidian, picket fence, sustained, quartan* and *saddleback fevers.* Such terms have been used to codify fever patterns into general categories in an attempt to enhance their diagnostic utility.

A few, such as the Pel-Ebstein pattern seen in some cases of Hodgkins's disease, the typhus inversus (i.e., reversal of the normal diurnal pattern) in some cases of disseminated tuberculosis, and the pulse-temperature disassociation sometimes seen in typhoid fever, have been posited as having diagnostic value (see figure 2). Accurate charting of the fever may require admission to hospital (16, 17).

Unfortunately, with the possible exception of the well-known periodicity of tertian and quartian malaria, these fever patterns are neither sensitive nor specific enough for diagnosis of any disease (16).

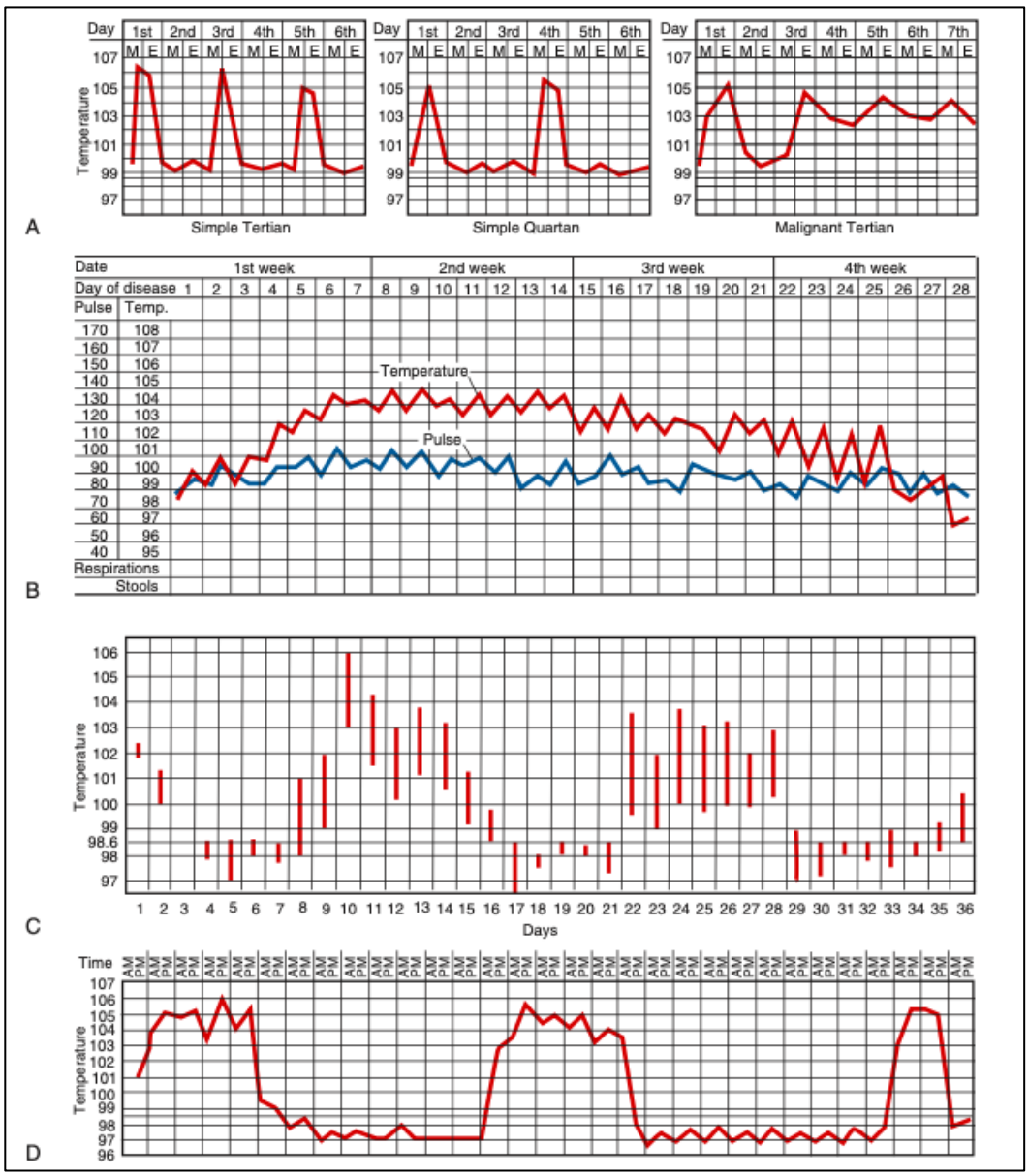


Figure 4. Distinctive fever patterns. A. Malaria. **B.** Typhoid fever (demonstrating relative bradycardia). **C.** Hodgkin's disease (Pel-Ebstein pattern). **D.** Borreliosis (relapsing fever pattern). (18)

A different type of fever that in its timing can be linked to the intake of certain types of drugs, is the drug-induced fever and the more urgent drug-induced hypersensitivity syndrome (DIHS). A whole array of pharmaceutical (e.g. beta-lactam antibiotics, anticonvulsants, anti-arrhythmics) and illegal drugs (e.g. cocaine or amphetamines) can cause this type of fever.

Pharmacological agents may cause fever by a number of different pathophysiological mechanisms. These include interference with the physiological mechanisms of heat loss from the peripheries, interference with central temperature regulation, direct damage to tissues, stimulation of an immune response, or pyrogenic properties of the drug. A common mechanism in many of these drugs is considered to be stimulation of non-shivering thermogenesis (NST), primarily in brown adipose tissue and skeletal muscle. Under normal conditions, cellular oxidative phosphorylation allows the synthesis of ATP from ADP for cellular metabolism. NST uncouples the proton movement from this pathway, allowing the energy to be dissipated as heat, under the control of uncoupling proteins, ultimately influenced by thyroid hormones and catecholamines. A number of agents, including sympathomimetics and those which act via the serotonin pathway, are thought to cause fever by modifying the NST pathway at a central, peripheral, or cellular level (13).

3.1.2.2 Exposure history and lifestyle factors

A comprehensive assessment of potential exposures can be of guidance in the diagnostic evaluation of FUO. This should include recent contact with infected individuals (e.g., tuberculosis), animal interactions (e.g., Q fever), and environmental or occupational risk factors (19, 20).

Environmental exposures may involve certain (unsanitary) living conditions, contact with infected or unvaccinated roommates, or others presenting with similar symptoms. Occupational risks include exposure to infectious agents or hazardous materials in professions such as farming, healthcare, or laboratory work can also play a role.

Additionally, recreational activities like camping or hunting may increase the risk of vector-borne diseases such as Lyme disease, while ownership of certain (especially exotic) pets may introduce the possibility of more uncommon infections.
Careful consideration of these factors is crucial for guiding appropriate laboratory investigations and optimizing the diagnostic approach (18).

3.1.2.3 Environmental factors

Multiple studies showed that all diagnostic outcomes of FUO were influenced by the geographical area where the study was performed. The risk of having an infection was more than 4 times higher in Southern Asia and 3 times higher in Far East Asia than in Europe. The diagnosis of NIID was more frequent in Middle East and Far East Asia than Southern Asia. The diagnosis of neoplasm was more frequent in the case-series from Southern Asia and middle East vs those from Far East Asia and Europe. The risk of having undiagnosed FUO was higher in Europe vs all other geographical areas (21-23).

These findings were confirmed by Wright *et al*. in their study from 2024 with the addition that patients from lower-middle-income countries were more likely than those from European and high-income countries to have an infectious disease rather than an NIID (6).

A study by Hassan *et al*. coincided by showing that across multiple developing countries, infectious disease was the most common cause of FUO (24).

One of the few studies from Africa, done by Kabapy *et al*., showed that in Egypt, infections remain the most common cause of FUO, followed by NIID (63.4% and 30.3% respectively) (10).

Wright *et al*. suggested that while some geographic regions lacked data for comparison, such as Africa and North and South America, the practical implications from these meta-analyses suggested that physicians worldwide should incorporate geographic disease prevalence when evaluating these patients (6).

Incorporating geographic disease prevalence requires acknowledging that travel, especially to high-risk regions, may expose patients to diseases endemic both to their country of origin and to the regions they have traveled to. The primary symptom reported in approximately 28% of post-travel medical consultations is fever. In any patient presenting with fever and a recent history of travel, particularly to tropical or subtropical regions, a detailed travel history is imperative. This should include the exact geographic locations visited, the duration and timing of travel, and any potential exposure risks encountered. Relevant risk factors include participation in activities such as swimming in freshwater bodies, trekking in forested or rural areas, and any direct or indirect contact with animals, as well as exposure to insect vectors (e.g., mosquitoes, ticks). These elements are critical in narrowing the differential diagnosis and identifying region-specific infectious diseases (25).

The main etiologies in these patients, especially those who travelled to tropical countries are: malaria (most common etiology), dengue, leptospirosis, rickettsiosis, salmonellosis, amoebiases, and schistosomiasis (16).

Endemic diseases should always be remembered at the time of the clinical investigation as they differ depending on location.
In a patient with post-travel fever from a malaria-endemic area, malaria should be excluded urgently, which means a patient should be referred to an emergency room.

3.1.2.4 Symptomatology

B-symptoms (weight loss, night sweats and fever) should always be questioned as these can be indicative for malignancies or tuberculosis.
In addition, associated symptoms such as jaundice, chronic cough or change in bowel movements should be carefully explored, since they can provide PDCs to infectious, neoplastic or inflammatory processes.

3.1.2.5 Medical and personal history

A thorough medical history including previous surgeries or diseases, known malignancies, autoimmune diseases, recent infections and frequency and severity of past infections. Comorbidities and ethnicity can also be of guidance, particularly in conditions with genetic or regional predispositions.

A detailed family history can also provide valuable indications of specific etiologies such as hereditary of autoimmune disorders that could explain the prolonged fever (25).

3.1.2.6 FUO categories

Each FUO category presents specific clues or PDC's that can stand out in the clinical history and guide towards more specified testing:

Infectious:

- (Sub)acute onset with night sweats and persistent fever
- History of recent travel to endemic regions (especially the tropics)
- Exposure to animals, insect bites (e.g. ticks, mosquitoes)
- Immunocompromised status (e.g. HIV/AIDS, post-transplant, chemotherapy) increases risk for opportunistic infections
- Localized symptoms: chronic cough (tuberculosis), abdominal discomfort (abscess), back pain (vertebral osteomyelitis)
- Indwelling devices (catheters, prosthetic valves, prosthetic joints, …) raise suspicion for device-associated infections like endocarditis

Neoplastic:

- B-symptoms (persisting fever, night sweating and unexplained weight loss)
- Fatigue and progressive symptoms over weeks to months, general malaise
- Painless lymphadenopathy or organomegaly (suggesting lymphoma or leukemia)
- History of smoking, occupational exposures, or family history of malignancy may be relevant

Rheumatological (NIID):

- Symmetrical joint pain, morning stiffness, and fatigue (e.g. rheumatoid arthritis)
- Fever, fatigue and proximal muscle pain (e.g. polymyalgia rheumatica)
- Headache, jaw claudication, vision changes (e.g. temporal arteritis (especially in patients >50 years old)
- Skin manifestations such as rash (typically butterfly rash), oral ulcers or photosensitivity can suggest systemic lupus erythematosus.

Miscellaneous:

- Medication induced fever: often overlooked, typically presents with fever unresponsive to antibiotics but resolving after stopping the offending agent (e.g. beta-lactam antibiotics, anticonvulsants, NSAIDs).
- Pseudo-fever or fictitious fever: inconsistent findings, fever patterns not matching physiologic norms, often in healthcare workers or those with access to thermometers or medications.
- Endocrine causes: thyrotoxicosis, adrenal insufficiency.
- Inherited syndromes: Familial Mediterranean Fever or other periodic fever syndromes; often seen in younger patients with recurrent attacks and specific ethnic backgrounds.
- Thromboembolic disease: pulmonary embolism may rarely present with FUO, particularly in elderly or immobilized patients.

3.1.3 Physical examination

A comprehensive full physical evaluation is essential when assessing a patient presenting with non-specific symptoms such as FUO. This general check-up should aim to identify any abnormal findings that may provide PDC and help guide further investigation and management.

The assessment must include a thorough examination of all major organ systems, with particular attention to the skin, oropharynx (with particular attention to dentition), heart, abdomen, lungs, lymph nodes and genitalia. These evaluations are critical in identifying subtle or overt signs that may otherwise be overlooked but are often indicative of underlying pathology (26, 27).

Frequently, key physical abnormalities in patients with FUO are so subtle as to require repeated examinations to be appreciated (18).

In table 1 a summary of the most important findings during physical examination is listed that can suggest potential etiologies of FUO. Most of these findings are only suggestive and warrant further examination or diagnostic work-up to diagnose them. They can however already guide the following choices of basic diagnostic testing.

On the contrary, some clinical findings, although rare, are virtually diagnostic, such as Roths spots in infective endocarditis (16).

Physical examination findings that suggest potential etiologies of FUO	
Finding	**Potential etiology**
Asymmetric pulse and/or blood pressure between extremities	Takayasu arteritis
Epididymal nodule	Extrapulmonary tuberculosis Periartritis nodosa Sarcoidosis Systemic lupus erythematosus
Fever peaks in the morning	Polyarteritis nodosa Typhoid fever Whipple disease
Fever with bradycardia (Facet sign)	Central nervous system malignancy Lymphoma Typhoid fever Yellow fever
Isolated hepatomegaly	Hepatic neoplasia Metastatic carcinoma Q fever Renal neoplasia
Lymphadenopathy	Lymphoma Rheumatoid arthritis Sarcoidosis Systemic lupus erythematosus Viral infections (EBV, HIV, CMV)
New heart murmur	Atrial myxoma Infective endocarditis
Oral ulcers	Behcet disease Periapical abscess
Petechiae	Vasculitis Endocarditis
Rash	Sarcoidosis Still's disease Systemic lupus erythematosus
Rectal tenderness	Abscess
Roth spots	Infective endocarditis
Sinus tenderness	Sinusitis
Spinal tenderness	Vertebral osteomyelitis
Splenomegaly	Cirrhosis Crohn disease Cytomegalovirus Epstein-Barr virus Miliary tuberculosis
Temporal artery tenderness	Giant cell arteritis
Thyroid enlargement/tenderness	Thyroiditis
Twice daily fever peak	Malaria Miliary tuberculosis Still's disease Visceral leishmaniasis

Table 1. Physical examination findings that suggest potential etiologies of FUO. Adapted from David et al. 2022 (28)

For example, the detection of a new heart murmur in the context of fever should raise suspicion for infective endocarditis, a potentially life-threatening condition that is notoriously difficult to diagnose and frequently under-recognized in early stages. Such murmurs may be the only initial sign of a serious intracardiac infection, and their presence warrants urgent follow-up with echocardiography and blood cultures (29).

The abdominal examination may reveal hepatomegaly (enlarged liver) or splenomegaly (enlarged spleen), both of which are key clinical signs that can point to a wide range of conditions, including viral infections (e.g. hepatitis viruses, Epstein-Barr virus, HIV), parasitic infections (e.g. malaria, leishmaniasis), and bacterial infections (e.g. typhoid fever). These findings may also be associated with hematological malignancies or autoimmune diseases, further emphasizing the need for a meticulous physical exam (30).

Additionally, the physician should actively search for signs of localized infection, such as tenderness in specific regions, lymphadenopathy, or organomegaly. These findings can be early indicators of systemic illness or localized abscess formation.

It is also important not to neglect a dermatological inspection, as the skin can provide vital diagnostic information. The presence of rashes, petechiae, or primary skin lesions (such as vesicles, pustules, ulcers, or maculopapular eruptions) can offer critical clues to the etiology of the illness. Certain rash patterns are characteristic of specific infectious diseases (e.g. measles, dengue, meningococcemia) or immunologic conditions (e.g. lupus, vasculitis), and their recognition can substantially narrow the differential diagnosis.

A well-conducted history and physical examination is perhaps more important than any other diagnostic procedure in focusing the FUO evaluation, accelerating initiation of appropriate therapy while minimizing the cost and potential toxicity of unnecessary testing and/or interventions.

3.1.4 Basic diagnostic testing

The initial laboratory work-up in patients with FUO should include a panel of nonspecific screening tests. When interpreted in conjunction with findings from the

clinical history and physical examination, these investigations can assist in formulating a focused differential diagnosis and identifying the most probable underlying etiology.

When formulating a diagnostic plan for FUO patients, the clinician should remember the old saying that the cause is more often a common disease presenting in atypical fashion than a rare disease presenting in typical fashion ("When you hear hoof beats, think horses not zebras"). Inappropriate diagnostic tests in the evaluation of FUO may not only delay identification of the correct diagnosis but also result in false-positive tests leading to misguided treatment plans (18).

The recommended first-line investigations typically include a complete blood count (CBC) with differential, markers of inflammation such as white blood cell (WBC) count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Additionally, evaluation of renal function (serum creatinine (Cr) and estimated glomerular filtration rate (eGFR)), thyroid function test consisting of thyroid-stimulating hormone (TSH) and thyroxine (T4), liver function tests consisting of alanine aminotransferase (ALT) , aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT), an electrolyte panel, as well as urinalysis and urine culture should be performed (31-35).

The literature however varies on the importance of certain markers of inflammation and their role in the work-up of FUO with ambiguous diagnostic significance.

A study by Naito *et al*. studied the usefulness of certain markers of inflammation and evaluated relationships between the causes of FUO and the levels of inflammatory markers in a general medicine hospital in Japan. They found that the rate of malignancy was significantly higher for a WBC count of <4,000/μL than for a WBC count of 4,000-8,000/μL. Among the patients with a higher WBC count, the rate of FUO due to NIID tended to be higher and the number of unknown cases tended to be lower. All FUO patients with malignancy showed an ESR of >40 mm/h. A normal ESR appeared to constitute powerful evidence for excluding a diagnosis of malignancy. In contrast, both the levels of CRP and procalcitonin appeared to be unrelated to the causative disease. A study by Bleeker-Rovers *et al*. did find that elevated CRP and/or ESR was an important factor in predicting the likelihood of reaching a diagnosis (31, 36).

Multiple studies compared the usefulness of procalcitonin in differentiating bacterial infection from non-infectious disease when compared to CRP. Naito *et al.* found that procalcitonin offers higher sensitivity (88%) and specificity (81%) than CRP (75% and 67%, respectively). Jabbour *et al*. found that elevated procalcitonin was a better inflammation marker than CRP, both in neutropenic and non-neutropenic patients and showed that it could better help distinguish between infectious and non-infectious etiology. Oka *et al*. showed that procalcitonin levels were positively correlated to CRP levels and ferritin levels as inflammation marker. Procalcitonin however was not only the best indicator for diagnosis of bacterial infection and/or sepsis, but also for the severity and prognosis of systemic inflammatory diseases. (31, 37, 38).

A study by Semeraro *et al*. investigated procalcitonin as an inflammatory marker as it is found to be more specific as a marker of infection than CRP, not for its diagnostic value, but for its prognostic value in predicting unfavorable or favorable outcome among patients hospitalized with FUO. They found that levels of procalcitonin were significantly higher in episode of unfavorable outcome with the best procalcitonin cut-off value at 0.12 µ/L, which was associated with a sensitivity of 80% and specificity of 64% (32).

Another inflammatory marker that is often mentioned when dealing with FUO is ferritin. It however also has its limitations as it has high sensitivity but low specificity. Elevated levels of ferritin are most often seen in certain neoplastic disorders (leukemia, lymphoma, …), rheumatic disorders (adult Still's disease, juvenile idiopathic arthritis, systemic lupus) and with (subacute) thyroiditis.

It should however always be combined with clinical context and other blood tests (CRP, ESR, liver enzymes) and imaging to help identify the cause of the FUO (17, 39-41).

Second-line investigations should be guided by clinical suspicion based on the integration of history, physical examination, and initial laboratory results. These may include serologic testing for viral infections (e.g. human immunodeficiency virus (HIV), viral hepatitis), rheumatoid factor (RF), antinuclear antibodies (ANA), serum ferritin, serum protein electrophoresis, lactate dehydrogenase (LDH), and pathogen-

specific serologies, including malaria blood smears or rapid diagnostic tests in the appropriate epidemiological context (25).

3.1.5 Naproxen test

The Naproxen test meets a lot of controversy among authors for its usefulness in the differential diagnosis of FUO. The test is based on the answer to the empirical therapy with a non-steroidal anti-inflammatory drug (most commonly naproxen) in patients with prolonged fever who have already had exhaustive investigations without finding an underlying cause. An etiology of infectious nature should be suspected in patients with no response to the empirical treatment, while in case of a response to the test in 24 hours a neoplasm should be suspected as the cause for the fever (8, 16, 42).

However, the theory that a patient's response to such drugs allows the doctor to fully differentiate neoplastic from other causes of unknown origin has been refuted (16).

3.1.6 Imaging exams

The choice of medical imaging can be similar to the choice of laboratory tests where we start with less specific (and cheaper) imaging before asking more specific testing.

A chest x-ray and ultrasound of the abdomen are among the first asked exams. They are both readily available to physicians and can easily be of guidance.

A chest x-ray can detect bigger abnormalities of the lungs and heart such as pneumonia, tuberculosis, lung masses, or pleural effusions, but also mediastinal lymphadenopathy. It can also hint toward smaller abnormalities that need to further be investigated with more detailed imaging.

An ultrasound of the abdomen has the same benefits as a chest x-ray in that it is very quick and easily available. It has the added benefit that it is non-invasive and radiation-free. It can evaluate the organs of the abdominal cavity such as the liver, spleen and kidneys and can evaluate lymph nodes as well. It is useful for detecting hepatosplenomegaly, abscesses or biliary disease.

Computed tomography (CT) of the abdomen has been used extensively to evaluate cases of FUO. In one series, more than three CT or ultrasound examinations, or both,

were performed for each FUO patient evaluated. Nevertheless, the diagnostic yield per test performed is low at about 10%. A study by Li *et al*. found that CT of the abdomen displayed a relatively low sensitivity but a high specificity. False-negative CT studies have occasionally been encountered, even in cases of abscesses in solid organs, as a result of distortions of normal anatomy, small abscess size, or failure to use both oral and intravenous contrast agents. CT pulmonary angiograms can be very helpful in diagnosis of pulmonary embolism (18, 43).

Magnetic resonance imaging (MRI) is a radiation-free option that is especially useful for evaluation of the central nervous system, the abdomen, the spleen and lymph nodes. In a series of 67 patients undergoing evaluation for FUO, Wagner *et al*. reported that application of MRI of the aortic arch and proximal cervical arteries in selected patients improved the diagnosis of large vessel vasculitis by 20%. Although one case did not demonstrate vasculitis changes by cervical imaging, four cases would have remained undiagnosed without the application of MRI. The most common diseases diagnosed by this testing modality were giant cell arteritis (55%), Takayasu's arteritis (27%), Wegener's granulomatosis (9%), and microscopic polyangiitis (9%). In another series involving prolonged fevers among neutropenic patients, MRI offered a reliable radiation-free option for diagnosing suspected pulmonary infections (18).

The utility of 18F-FDG PET/CT in FUO remains debated. Earlier studies reported variable results; however, more recent analyses have shown promising outcomes. In a prospective comparison, Meller *et al*. reported a sensitivity of 81% and a specificity of 86% for FDG-PET in detecting the source of fever. A meta-analysis by Dong *et al*. found pooled sensitivity and specificity values of 98.2% and 85.9%, respectively, in diagnosing FUO etiologies. Sensitivity varied by category: 86.7% for malignant neoplasms, 81.5% for infectious diseases, and 76.3% for noninfectious inflammatory conditions. 18F-FDG PET/CT was particularly useful for detecting localized abscesses, osteomyelitis, sinusitis, sarcoidosis, vasculitis, adult-onset Still's disease, Crohn's disease, and subacute thyroiditis (18).

A study by Liu *et al*. confirmed these findings showing that 18F-FDG PET/CT has a high diagnostic accuracy and significant impact on patient management. The results from 18F-FDG PET/CT contributed directly to change in inpatient management in 98% of the cases, with 83% of studies contributing directly to the identification of the final

FUO diagnosis. 18F-FDG PET/CT performed earlier in admission for FUO was also associated with shorter length of stay and lower total cost of admission (44).

A different study by Olianti *et al*. regarding the use of 18F-FDG PET/CT in diagnosing FUO in pediatrics found that pediatric FUO patients with abnormal PET findings were 17 times more likely to achieve definite diagnoses than those with normal PET findings, independent of FUO subclasses and geographical areas of studies (45).

Expert consensus panels recommend that, when available, 18F-FDG PET/CT may serve as an important early diagnostic tool once FUO criteria have been fulfilled and minimal diagnostic tests completed, particularly in the absence of clear PDCs (6).

The 18F-FDG PET/CT appears to have an added value in the diagnostic work-up of FUO, however the place to perform this is not in primary care.

3.1.7 Empirical treatment and referral

In most clinically stable cases of FUO, empirical treatment is considered to be unnecessary. This therapy should be reserved for those in life-threatening condition, clinically unstable or neutropenic patients whose diagnostic evaluations has been exhausted and when a clinician believes the illness warrants such therapies instead of observation. In this case, empirical treatment may be lifesaving (6, 25).

Empirical treatment, when unavoidable, may include anti-inflammatory agents (including corticosteroids), antibiotics or both and can be assisted with supportive care (16).

Patients that require immediate referral to hospital:

- Immunocompromised
- Post malignancy or transplant
- Post travel with fever from non-malaria endemic regions for more than 3 days
- Post travel with fever coming from malaria-endemic regions: immediate referral to an emergency room
- Organ failure or sepsis
- Clinically unstable

(46)

3.1.8 Algorithm

Based on the literature study we propose the following algorithm in the workup of FUO:

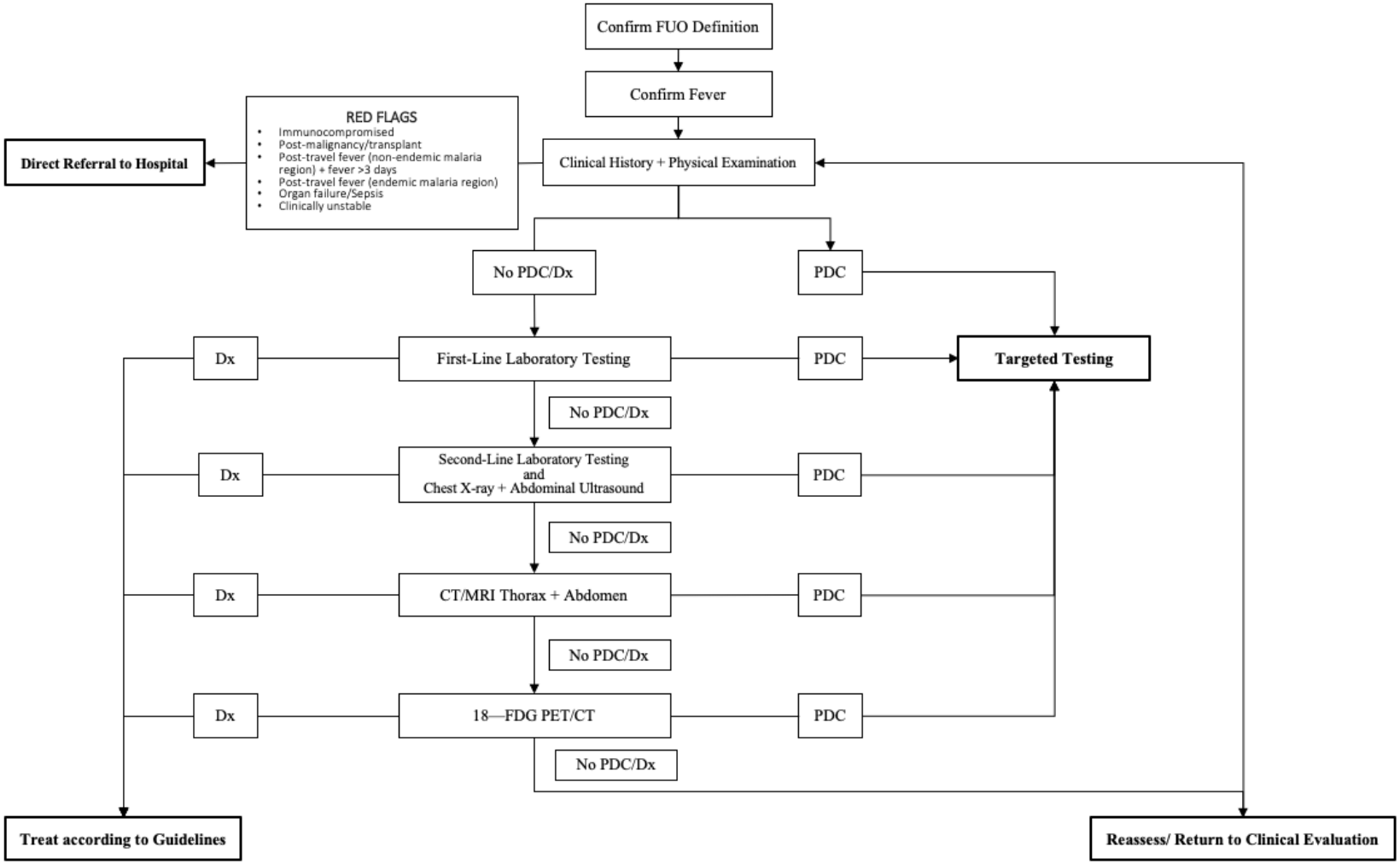


Figure 5. Algorithm; PDC = Potential diagnostic clues, Dx = Diagnosis, First-Line Laboratory Testing: CBC, WBC with differentiation, CRP and ESR, Cr, eGFR, ALT, AST, GGT, TSH, T4, electrolyte panel, urinalysis and urine culture

4 Discussion

4.1 Summary of main results

FUO remains a challenging diagnostic problem, as it can be caused by a wide range of conditions and can fool even the most experienced physicians. This wide differential diagnosis causes the difficulty in determining the appropriate diagnostic tools and to streamline the approach of FUO.

4.1.1 Physical examination

The literature strongly underlines the importance of the physical examination when dealing with the management and diagnosis of FUO, yet the diagnostic yield of the physical examination itself has not been studied directly (18).

None the less, physical examination is a repeated process which can help generate hypothesis and determine probability of diagnosis when proceeding with further diagnostic tests. It helps narrow the differential, can detect high-specificity clues, direct efficient testing and can prevent unnecessary investigations.
Many classic FUO diagnoses are ultimately made because the physical examination was carefully repeated and re-evaluated.

4.1.2 Laboratory tests

The basic work-up of FUO is quite commonly accepted as a CBC with differential, markers of inflammation, evaluation of renal function, thyroid function test, liver function tests, an electrolyte panel, as well as urinalysis and urine culture (31-35).

The literature however varies on the importance of certain markers of inflammation and their role in the work-up of FUO with ambiguous diagnostic significance. As discussed in results, there are multiple markers of inflammation available, each with specific importance and usefulness. The most commonly used markers of inflammation are CRP and WBC, both of which have a high sensitivity but highly variable specificity as to not miss any diagnosis of inflammation. They do however lack the specificity to help narrow down the differential diagnosis of patients with FUO.

A whole array of other inflammation markers with differing sensitivity and specificity are also available to the primary care physician such as ESR, procalcitonin and ferritin. Studies have found that these can not only have higher levels of sensitivity and specificity when used as marker of inflammation but can also be of use when determining the severity of inflammation, prognosis of systemic inflammatory diseases and prognostic value in predicting unfavorable or favorable outcome (17, 31, 32, 36-41).

The second-line investigations should be guided by clinical suspicion based on the integration of history, physical examination and initial laboratory results.
If PDC's are present, guided diagnostic testing should be performed to further investigate these clues. These may include serologic testing for viral infections (e.g. human immunodeficiency virus (HIV), viral hepatitis), rheumatoid factor (RF), antinuclear antibodies (ANA), serum ferritin, serum protein electrophoresis, lactate dehydrogenase (LDH), and pathogen-specific serologies, including malaria blood smears or rapid diagnostic tests in the appropriate epidemiological context (25).

4.1.3 Imaging exams

The literature consistently supports the use of chest x-ray and ultrasound of the abdomen as initial imaging for evaluating FUO as part of the basic work-up. Both of these can also more easily be interpreted, with the help of a radiologist, by a primary care physician, before referral to a hospital is necessary.

However, the role and/or timing of more advanced imaging techniques such as CT, MRI and 18F-FDG PET/CT remains the subject of considerable debate.

For this study we also did not find any guidance on when or whether the patient should be referred to a hospital for further imaging and at what point the interpretation of the imaging can no longer adequately be evaluated by a primary care physician. Additionally, in certain countries such as Belgium 18F-FDG PET/CT is only reimbursed when prescribed by a hospital specialist and not by a primary care physician.

As stated by Naito *et al*. many studies have proven 18F-FDG PET/CT to be a useful test to evaluate patients with FUO as all showing a percentage of helpfulness that

exceeds that of CT, MRI or other diagnostic possibilities (33).

The study by Bleeker-Rovers *et al*. confirms this by proving that an abnormal 18F-FDG PET/CT was a significant predicting factor for reaching a diagnosis. This in contrary to either chest X-ray, abdominal ultrasound or CT, where an abnormal result was not predictive of reaching a diagnosis (36).

A review by Takeuchi *et al*. investigated the use of nuclear imaging for classic FUO and concluded that 18F-FDG PET/CT was the most promising nuclear test with the highest diagnostic yield. They immediately countered this by stating that little is known about the impact of all nuclear imaging tests on diagnostic and therapeutic decisions, stating that future studies should use designs with a prespecified diagnostic algorithm before nuclear imaging (47).

4.1.4 Empiric treatment and referral

Empiric treatment should be reserved for those in life-threatening condition, clinically unstable or neutropenic patients whose diagnostic evaluations has been exhausted and when a clinician believes the illness warrants such therapies instead of observation. This to avoid the possible negative effects upon establishing a final diagnosis (e.g. corticosteroids can delay or impair the diagnosis of lymphoma) or adverse drug reactions. To date, no study has evaluated the predictive value of withholding or initiating empirical treatments and subsequent outcomes (6, 48).

It should however be noted again that certain types of patients need an immediate referral to a hospital:

- Immunocompromised
- Post malignancy or transplant
- Post travel with fever from non-malaria endemic regions for more than 3 days
- Post travel with fever coming from malaria-endemic regions: immediate referral to an emergency room
- Organ failure or sepsis
- Clinically unstable

(46)

4.1.5 Reflection

A reflection on the proposed algorithm shows that it does have its limitations.

First, it is not exactly determined at what point a patient with FUO has to be referred to a hospital or whether or not it can still be managed by a primary care physician. When any red flags are present, it is clear that a referral to a hospital is necessary. The same applies to when more specialized medical imaging is necessary, as this can sometimes only be prescribed by certain hospital specialists.

Everything in between is a grey area as it depends on the primary care physician and the amount of testing and specialty of testing he or she feels comfortable with. When a PDC is present and targeted testing is recommended, the primary care physician will sometimes notice that not all testing can be done in primary care setting and referral to a hospital is necessary for the testing itself. This however does not mean that the primary care physician cannot still diagnose and potentially treat the cause of the FUO once testing has been completed.

Second, it should be noted that the algorithm remains quite simple, despite FUO being a very complicated pathology. This is as to not recommend wild goose chases in which all arrays of testing are done without any regard for logic or diagnostic reasoning. This unreasoned testing can more often be confusing than it is clarifying as all tests have their limitations. False positives or false negatives can send the diagnostic reasoning on a whole new path which does not help the diagnosis itself.

Third, primary care physicians should take into consideration that the proposed algorithm is a guide-line and does not have to be followed to the exact. If for example there is a strong suspicion of a potentially dangerous pathology, it can be more suited to discuss with a hospital specialist or refer to hospital, with only a limited set of testing already done. In the best interest of the patient, it is advised to diagnose and treat this potentially dangerous pathology as soon as possible.

5 Conclusion

5.1 Implications for practice

This thesis emphasizes that a systematic, step by step approach remains the key to a correct diagnosis when dealing with FUO. Even in an era of overwhelming options of diagnostic tests and imaging, careful clinical reasoning remains the foundation of good diagnostic practice. These tools can support, but should not replace, methodical history taking, physical examination and logical differential diagnostic approach. Rare or atypical diseases should be considered when common causes of FUO have been excluded.

The timely referral or collaboration with hospital specialists is still of the utmost importance as this can help guide the physician in the diagnostic work-up and help streamline this process. The exact timing however, remains to be discussed.

5.2 Implications for research

Limited data is available for the approach of FUO in primary care setting. Almost all studies have been done in hospital setting with an abundance of possible diagnostic tests which are not always available to primary care physicians on such short notice. This data can be subtracted to general practice, but remains uncertain about timing and necessity of referral to hospital.

More studies, specifically to diagnosing FUO in primary care or on the timing and importance of referral to a hospital, should be done in general practice setting.

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