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REVIEW ARTICLE

Fever and Fever of Unknown Origin: Review, Recent Advances, and Lingering Dogma

William F. Wright[1] and Paul G. Auwaerter[2]

[1]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine Baltimore, Maryland, USA, and [2]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Fever has preoccupied physicians since the earliest days of clinical medicine. It has been the subject of scrutiny in recent decades. Historical convention has mostly determined that 37.0°C (98.6°F) should be regarded as normal body temperature, and more modern evidence suggests that fever is a complex physiological response involving the innate immune system and should not be characterized merely as a temperature above this threshold. Fever of unknown origin (FUO) was first defined in 1961 by Petersdorf and Beeson and continues to be a clinical challenge for physicians. Although clinicians may have some understanding of the history of clinical thermometry, how average body temperatures were established, thermoregulation, and pathophysiology of fever, new concepts are emerging. While FUO subgroups and etiologic classifications have remained unchanged since 1991 revisions, the spectrum of diseases, clinical approach to diagnosis, and management are changing. This review considers how newer data should influence both definitions and lingering dogmatic principles. Despite recent advances and newer imaging techniques such as 18-fluorodeoxyglucose–positron emission tomography, clinical judgment remains an essential component of care.

Keywords. clinical thermometry; fever; fever of unknown origin; pyrexia; pyrexia of unknown origin.

Humanity has but three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever.

William Osler

Concepts of fever have changed over the past millennia, dating from the earliest known fever curves created by the 10th-century BCE Persian physician Akhawaynī [1]. He authored the medical compendia *Hidāyat al-Muta'allimīn fī al-Tibb* (*The Student's Handbook of Medicine*), defining a system for fever curves including descriptions of tertian, quartan, double tertian, double quartan, and triple quartan fevers hundreds of years before they were routinely used in clinical settings. Akhawaynī's theory for the pathogenesis of fever subsequently influenced the basis for the humoral theory of fifth-century Greco-Roman physicians. Since attributed to Hippocrates of Kos (460–377 BCE), *pyretos* and *therme* (fever and heat) arose from an imbalance (or dyscrasia) of the 4 corporal elements—sanguis (blood), *flegma* (phlegm), *melanchole* (black bile), and *chole* (yellow bile)—in which there existed an excess of yellow bile [1, 2]. Hippocratic physicians detected elevations in body temperature by palpation and recognized the association of fever with an accelerated pulse rate [1, 2].

Claudius Galen of Pergamum (131–201 CE) refined these concepts sufficiently such that they dominated medical thinking for over a thousand years [1, 2]. He regarded fever as a disease itself, rather than a sign of disease. Humoral imbalances were thought to stem from factors including putrefaction, proximity to an external source of heat, constriction, or certain foods capable of producing heat (eg, garlic, leeks, and onions). The Romans of his era believed that at least some cases of fever were the work of the goddess Febris, to whom they dedicated a temple on Palatine Hill to propitiate her [1, 2].

Given this history and the prominence of Galileo, Fahrenheit, and Celsius in the history of the development of the thermometer, one may believe that clinical thermometry emerged fully formed from the heads of these great men [2]. Another assumption could lie in thinking that the thermometer's birth occurred not long after clinicians recognized that monitoring body temperature could ferret out disease from among the many aches and minor perturbations of an otherwise healthy existence. However, as is usually the case with discoveries and inventions, the seeds were planted and then nurtured by many others long before those receiving credit for their contributions. From today's perspective, one man stands by far as the most influential in fostering thermometry for clinical applications. In 1868, the German physician Carl Reinhold August Wunderlich (1815–1877) published the magnum opus *Das Verhalten der Eigenwärme in Krankheiten* (*The Course of Temperature in*

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Correspondence: William F. Wright, DO, MPH, Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, 733 North Broadway, Baltimore, MD 21205 (wwrigh19@jhmi.edu).

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Diseases) that persists today as the foundational work on the subject. The findings galvanized 98.6°F (37.0°C) as an average normal body temperature [1, 3]. This conclusion was derived from over a million axillary temperature readings taken from some 25 000 patients and offered the first quantitative definition of fever as 100.4°F (38.0°C) or higher [1, 3, 4].

Clinical thermometry in America was introduced in the mid-1860s by Édouard Séguin (1812–1880), an avowed disciple of Wunderlich [5]. Although many have sought to verify Wunderlich's conclusions since 1935 [6], a rigorously conducted study of normal body temperature was published in 1992. Seven hundred temperature recordings taken from 148 healthy volunteers recruited for vaccine trials were reported by Mackowiak and colleagues [4]. Using an electronic oral thermometer, they described 36.8°C (98.2°F) rather than 37.0°C (98.6°F) as the normal mean oral temperature and 37.7°C (99.9°F) rather than 38.0°C (100.4°F) as the upper limit of the normal range. Circadian temperatures varied by a mean average of 0.5°C (0.9°F) between 6 AM (nadir) and 4–6 PM (zenith). These authors also reported slightly higher temperatures among women and African Americans. Differences between modern and historical values likely also lie in factors such as instrument design, assessment location (axillary, oral, or rectal), time needed for equilibration, and thermometer reading methods, as suggested by Mackowiak and colleagues to partly explain differences from Wunderlich's conclusions. Other investigators, using mercury-in-glass thermometers among 184 healthy individuals, reported average oral temperatures ranging from 36.1°C (97.0°F) to 37.7°C (99.8°F) [7]. They found that axillary temperatures were lower than the oral temperature by an average of 0.85°F and confirmed that women had higher body temperatures than men.

A recent study by Protsiv and colleagues [8] analyzed 677 423 human body temperature measurements from 3 different cohort populations spanning 157 years. These investigators reported that mean body temperatures in men and women, after adjusting for age, height, and weight, have decreased monotonically by 0.03°C per birth decade since the 1890s. The authors postulated that undiagnosed chronic infections such as tuberculosis, syphilis, and other causes of chronic inflammation might well have influenced the "normal body temperature" of Wunderlich's era. They also hypothesized that potential physiologic changes in the modern population, who are generally taller and heavier than earlier times, might contribute.

The introduction of clinical thermometry was contemporaneous with Louis Pasteur's (1822–1895) discoveries heralding the golden age of bacteriology [9]. A prime challenge then developed: What was the cause of fever? Throughout the 20th century, most causes of fever were either self-limiting or readily diagnosed with evolving technologies. Despite the miracles of many medical advancements, a small subgroup of fevers are both persistent and challenging to diagnose. Termed "fevers of unknown origin" (FUO), these suffering patients have fascinated and frustrated clinicians since the earliest days of clinical thermometry.

The first formal definition of FUO to gain broad acceptance was proposed by Petersdorf and Beeson nearly 6 decades ago: "fever higher than 38.3°C (100.9°F) on several occasions, persisting without diagnosis for at least 3 weeks in spite of at least 1 week's investigation in hospital" [9]. With subsequent advancements in medical care, Durack and Street [10] offered a 1991 revised definition for the now so-called classical FUO offered by Petersdorf and Beeson to include a proviso for patients with an uncertain diagnosis despite 3 days in the hospital or 3 outpatient visits. Building upon the classical FUO category, they also outlined 3 additional groups of FUO: nosocomial (health care–associated), neutropenic (immune-deficient), and HIV-related (Table 1) [10]. This nosology remains widely used today. However, technically, fevers at initial evaluation are usually of unknown origin until associated with a likely or definitive diagnosis. Petersdorf and Beeson developed the FUO categorization to refer to a particular subset of fevers that defied diagnosis after a reasonable workup.

As fever is a common condition encountered by nearly all practicing clinicians, newer evidence makes a strong case that

Table 1. Fever of Unknown Origin Definitions

Type	Definition
Classic	Temperature >38.3°C (100.9°F) recorded on several occasions occurring for >3 weeks in spite of investigations on 3 outpatient visits or 3 days of stay in the hospital or 1 week of invasive ambulatory investigations.
Nosocomial	Temperature >38.3°C (100.9°F) recorded on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest or incubating on admission. Three days of investigations including at least 2 days incubation of cultures is the minimum requirement for this diagnosis.
Neutropenic	Temperature >38.3°C (100.9°F) on several occasions observed in a patient whose neutrophil count is <500/μL or expected to fall to that level in 1–2 days. This diagnosis should be considered for investigations including at least 2 days of incubation of cultures. This is also called immunodeficient FUO.
HIV-associated	Temperature >38.3°C (100.9°F) on several occasions found over >4 weeks or >3 days for hospitalized patients with HIV infection. This diagnosis is considered if appropriate investigations over 3 days, including 2 days of incubation of cultures, reveal no source.

Adapted from Durack and Street [10].

Abbreviation: FUO, fever of unknown origin.

concepts of fever and changes within FUO investigations should be reevaluated in our contemporary medical practice to make appropriate and timely interventions for patients. This article briefly reviews updates to thermoregulation physiology and new concepts within innate immune-mediated mechanisms of infection-associated fever. Given space limitations, further review of FUO etiologies will be limited more to the classical FUO category, with some mentions of certain special populations, diagnostic approaches, and management considerations.

Thermoregulation and the Febrile Response

William Harvey's (1578–1657) experiments noted in *On the Circulation of the Blood* (1628) led contemporary iatrophysicists and iatrochemists to hypothesize that body heat resulted from blood flow friction, fermentation, and putrefaction throughout the vascular and gastrointestinal systems [11]. French physiologist Claude Bernard's (1813–1878) work advanced understanding of cellular biochemical reactions and carbohydrate metabolism, leading to the source of body heat [11]. Classically, thermophysiologists posited a model wherein the preoptic region of the brain located near the rostral hypothalamus served as a temperature-sensitive region, providing regulation within a narrow range of temperatures derived from thermosensors in the skin and core regions [11–14]. This model holds that skin and core receptors transform temperatures into neuronal firing rates decoded in the brain by the labeled line hypothesis (eg, a particular stimulus is generated from all sensory cells activated by that stimulus) [11, 12, 14]. The labeled line hypothesis predicts that individual receptor cells will respond to only a single temperature quality; therefore, the function of any single neuron in an afferent pathway is to signal its particular encoded temperature quality.

Based on patch-clamp and knockout mice analyses of temperature-sensitive receptors, a new model proposes that nerve ending temperature receptors depolarize through voltage-gated sodium channels to act as thermostat molecules that compare whether the skin temperature is below a whole-cell set-point (eg, 25°C) and generate thermal error-dependent nerve impulses as command signals rather than a sensory code [12]. Thermoregulatory behaviors (eg, brown adipose tissue thermogenesis, shivering, sweating, vasoconstriction, and vasodilatation) are currently thought to be regulated by a set of relatively independent thermoeffector control loops using both feedback and feedforward neurological signals in response to both changes of core and skin temperatures [12, 13].

According to the view of infection-associated fever, induction occurs in an incremental fashion. In the example of bacterial infection–associated fever, this begins with exposure to an exogenous pyrogen (eg, bacterial lipopolysaccharide [LPS], also known as endotoxin) from a pathogenic microorganism, followed by the release of endogenous pyrogens (eg, interleukin ([L]-1, IL-6, tumor necrosis factor (TNF), and interferons [IFNs], collectively referred as pyrogenic cytokines) from host innate immune cells [11, 14, 15]. Endogenous pyrogens, in turn, are transported via the bloodstream to the preoptic region, where fever is generated by local production of prostaglandin E_2 (PGE_2) from central thermoregulatory vascular endothelial cells and neurons [11, 15]. Noradrenaline release by PGE_2 receptor 3 (EP3)–expressing sympathetic nervous system neurons then results in vasoconstriction and brown adipose tissue thermogenesis [15, 16]. Acetylcholine contributes to fever through muscle myocyte–induced shivering [16]. This pathogenic model also involves an early fever phase resulting from peripherally produced PGE_2, mediated predominantly by activation of pulmonary and hepatic macrophages, and less so by dendritic cells, through recognition of LPS by pattern recognition receptors (PRRs), such as Toll-like receptor 4 (TLR-4) [15, 16]. A late fever phase is mediated through both peripheral and central PGE_2 production [15, 16]. Fever, therefore, is currently viewed as a thermoregulatory manifestation of the innate immune responses in the setting of bacterial infection (Figure 1) [15, 16].

Classic FUO Spectrum of Disease

Of the many publications concerning the etiology of FUO [9, 17–30], most have dealt with classic FUO rather than with the 3 other more recently defined subclasses listed earlier [10]. Over the years, an organizing principle has become firmly established. Of the myriad disorders causing classic FUO, all etiologies may be grouped within 1 of 5 categories: infection, neoplasia, inflammatory (eg, rheumatologic or connective tissue diseases), miscellaneous diseases, and undiagnosed illness (Table 2). The relative frequencies of individual diagnoses within these 5 categories vary depending on the decade, geographic region, age of the patients, and type of medical practice.

In more recent series, infections have continued to comprise a significant percentage of FUO cases, accounting for 16%–55% of cases (Table 2) [31]. Compared with 70 years ago, infections and miscellaneous causes are less commonly an FUO explanation in industrialized countries, whereas the proportion of undiagnosed conditions has risen. Among the infections responsible for classic FUO, abscesses, endocarditis, tuberculosis, and complicated urinary tract infections have consistently been among the most frequently diagnosed (Table 3). Although the distribution of diagnostic categories was similar among developed vs developing countries in modern series, urinary tract infections, brucellosis, tuberculosis, and typhoid fever were more commonly identified in developing countries. The most common infections diagnosed in cases of FUO in developed countries included urinary tract infections, osteomyelitis, tuberculosis, and bartonellosis (eg, *Bartonella henselae*). However, in many series in patients aged >65 years, infections become less frequent, falling into second or third place as a cause of classic FUO [19, 30].

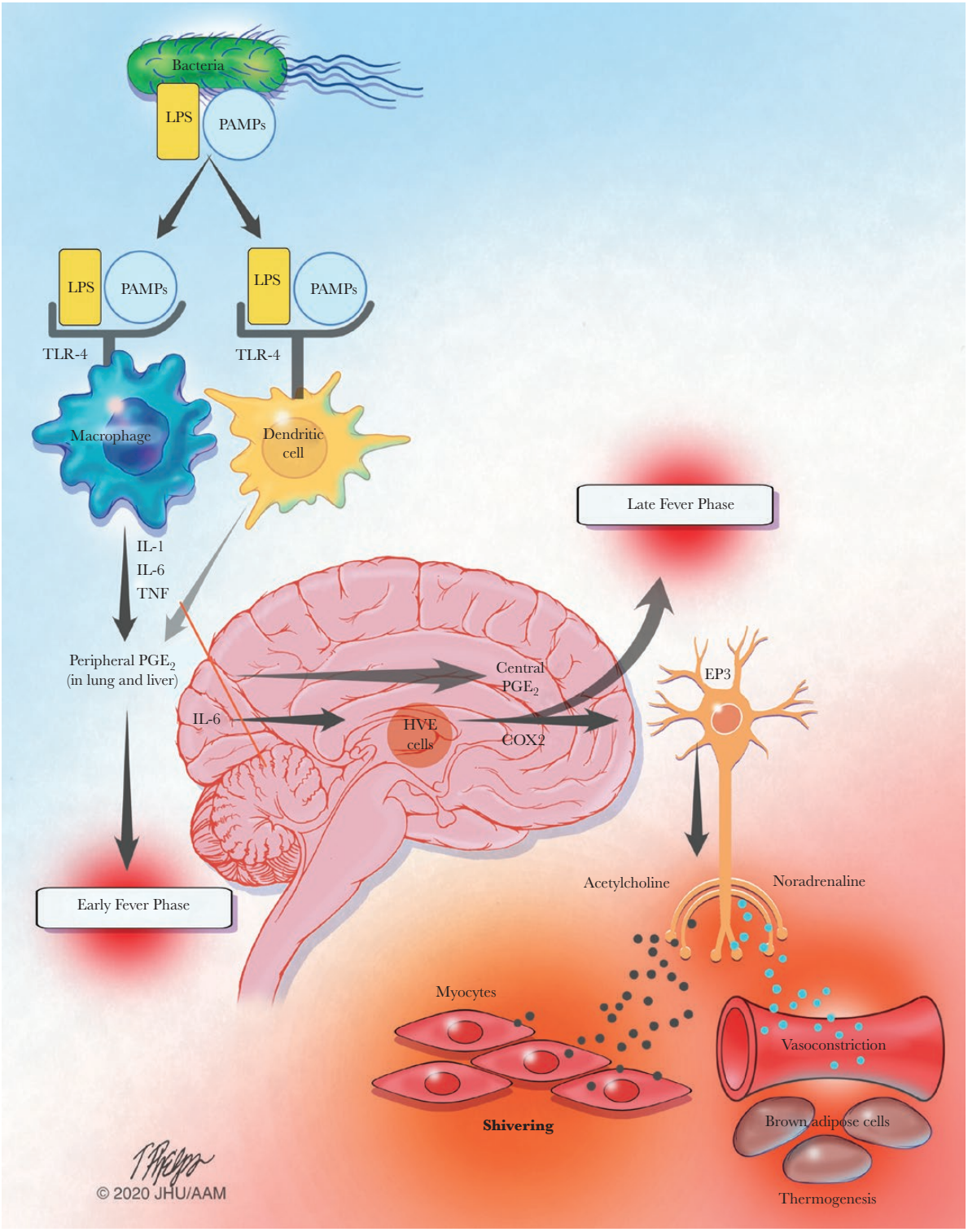

Figure 1. Innate immunity hypothesis of bacterial infection–associated fever. Microbial products (such as bacterial LPS) or PAMPs are recognized by cellular PRRs, such as TLR-4, on macrophages and dendritic cells. The early fever phase involves activation of these immune cells (predominantly macrophages) within the lung and liver ~30 minutes after LPS exposure, causing the release of PGE_2 as well as pyrogenic cytokines (such as IL-1, IL-6, and TNF). IL-6 induces HVEs to produce cyclooxygenase 2 and additional PGE_2. Together, both central production and peripheral production of PGE_2 cause a late fever phase ~90 minutes after LPS exposure. Consequently, while peripherally synthesized PGE_2 acts to initiate the febrile response before its migration to the brain, centrally produced PGE_2 is primarily involved in fever maintenance. EP3-expressing neurons then trigger the release of noradrenaline from the sympathetic nervous system, resulting in vasoconstriction and brown adipose tissue thermogenesis. Release of acetylcholine contributes to fever by muscle myocyte–induced shivering [15, 16]. Abbreviations: COX2, cyclooxygenase 2; EP3, PGE_2 receptor 3; HVEs, hypothalamic vascular endothelial cells; IL-1, interleukin-1; LPS, lipopolysaccharide; PAMPs, pathogen-associated molecular patterns; PGE_2, prostaglandin E_2; PRRs, pathogen-associated molecular patterns; TLR-4, Toll-like receptor 4; TNF, tumor necrosis factor.

Table 2. Frequencies of Diagnoses Within the 5 Categories of Classical Fever of Unknown Origin From Selected Publications

Publication (Year) [Ref]	Total No. of Patients	Infection, %	Neoplastic, %	Inflammatory, %	Miscellaneous, %	Undiagnosed, %
Petersdorf (1961) [9]	100	36.0	19.0	19.0	19.0	7.0
Petersdorf (1980) [17]	105	30.0	31.0	17.0	10.0	12.0
Larson (1982) [18]	105	30.0	31.0	16.0	11.0	12.0
Knockaert (1992) [19]	199	22.6	7.0	21.5	14.5	25.6
Barbado[a] (1992) [20]	218	11.0–31.0	18.0–28.0	13.0–29.0	17	15.0–21.0
Kazanjian (1992) [21]	86	33.0	24.0	26.0	5.0	9.0
De Kleijn (1997) [22]	167	26.0	12.0	25.0	8.0	30.0
Vanderschueren (2003) [23]	192	29.7	35.4	15.1	19.8	51.0
Saltoglu (2004) [24]	87	17.2	18.3	13.7	2.2	7.0
Ergonul (2005) [25]	80	52.0	19.0	17.0	3.0	12.0
Bleeker-Rovers (2007) [26]	73	16.0	7.0	22.0	4.0	51.0
Colpan (2007) [27]	71	45.1	14.1	26.8	5.6	8.5
Mansueto (2008) [28]	91	31.8	14.2	12.0	9.8	31.8
Bandyopadhyay (2011) [29]	164	55.0	22.0	11.0	3.5	8.5
Naito (2019) [30]	141	17.0	15.6	34.0	12.1	21.3

[a]The report by Barbado and colleagues consisted of 2 series: (a) 133 patients from 1968–1981 and (b) 85 patients from 1982–1989 [20].

In the Dutch series of Knockaert and associates [19], infection was the cause of FUO in only 25% of cases aged 65 years or older; various inflammatory diseases accounted for 31% of cases, and malignancy accounted for 12%. Of the inflammatory diseases responsible for classic FUO, adult-onset Still's disease (juvenile rheumatoid arthritis), other variants of rheumatoid arthritis, and systemic lupus erythematosus predominate in younger patients, whereas temporal arteritis and polymyalgia rheumatica syndromes are more common in elderly patients [30, 31]. Only 8% of cases went undiagnosed, which was similar to the percentage reported by Colpan and colleagues [27] but substantially lower than that reported in surveys involving younger adults, in which as many as 32% of cases remain undiagnosed [28].

Malignant neoplasms, another important cause of FUO, can induce fever directly through the production and release of pyrogenic cytokines, as in the case of certain lymphomas [11]. They may also generate fever indirectly by undergoing induced or spontaneous necrosis or by creating conditions conducive to secondary infections. Among the malignant and nonmalignant neoplasia responsible for FUO, leukemia, lymphoma (including Hodgkin and non-Hodgkin types as well as Castleman's disease), multiple myeloma, myelodysplastic syndrome, hypernephroma, and gastrointestinal cancers (mainly colorectal cancers) have been documented as common causes [9, 17, 18, 31].

In comparison with adult FUO series, the pediatric population likely experiences FUO less frequently, and fewer studies have examined this subject. Chow and Robinson [32] analyzed 18 papers concerning pediatric FUO published between 1968 and 2008. Of 1638 children, from birth to 18 years, 832 (51%) had infections, 93 (6%) had malignant neoplasms, 150 (9%) had noninfectious inflammatory diseases, 179 (11%) had miscellaneous causes such as inflammatory bowel disease and Kawasaki disease, and 384 (23%) had no diagnosis. In a more recent publication, Zhou and colleagues [33] investigated the presence of 7 different herpesvirus types in whole blood from pediatric patients with classic FUO. Of 151 children aged 6 months to 15 years, 63 (33.9%) had detectable herpesvirus DNA. Cytomegalovirus (CMV; 15.1%), human herpesvirus-6 (HHV-6; 14%), and Epstein-Barr virus (EBV; 18%) were the viruses detected most commonly when compared with a nonfebrile cohort. Whereas fever alone occurred in the majority of these patients, fever of at least 8 days' duration and hepatitis were more strongly associated with EBV and HHV-7. It is unclear whether these viruses are the primary cause of FUO in all patients or if the findings are simply the result of detectable levels

Table 3. Examples of Common and Uncommon Causes of Prolonged Fever [26, 27, 30, 31, 33–35]

Category	Common	Uncommon
Infectious diseases	Mycobacterium tuberculosis (mainly extrapulmonary) Endocarditis, culture-negative Epstein-Barr virus infections Cytomegalovirus infections	Bartonellosis (mainly *Bartonella henselae*) Brucellosis Occult abscesses Salmonellosis Urinary tract infections Acute HIV Hepatitis A, B, and E Human herpesvirus-6 Human herpesvirus-7 Bone and joint infections
Neoplastic diseases	Lymphoma (Hodgkin and non-Hodgkin) Leukemia Solid-organ tumors (renal cell carcinoma and melanoma)	Myelodysplastic syndrome Colonic adenocarcinoma Multiple myeloma Gastric carcinomas Mesothelioma Castleman's disease
Inflammatory diseases	Adult-onset Still's disease Systemic lupus erythematosus Polymyalgia rheumatica Temporal arteritis Inflammatory bowel disease	Rheumatoid arthritis Polyarteritis nodosa Sarcoidosis Granulomatosis with polyangiitis Still's disease Kawasaki's disease
Returned travelers	Malaria Dengue virus	Pulmonary infection Urinary tract infections Hepatitis A, B, and E Rickettsial diseases Leptospirosis Schistosomiasis Gnathostomiasis Cysticercosis Typhoid Acute HIV Tuberculosis
Miscellaneous	Medication/drug fever[a] Chronic pulmonary embolism Hyperthyroidism Hematoma	Subacute thyroiditis Hypoadrenalism Necrotizing lymphadenitis Periodic fevers (genetic) Hemophagocytic lymphohistiocytosis Factitious fever[b]

[a]Medications can cause fever through various mechanisms and include many classes such as antimicrobials, anticholinergics, urate-lowering agents (eg, allopurinol), nonsteroidal anti-inflammatory agents, antiarrhythmics, first-generation anticonvulsants, and antidepressants.

[b]Factitious (self-induced) fever can be caused by a range of psychiatric or nonexisting illnesses (eg, Munchausen syndrome, Munchausen syndrome by proxy, malingering, and various personality disorders) and is more common among individuals with a medical background such as doctors, nurses, pharmacists, and/or laboratory technicians.

of reactivated latent viruses in association with another physiologically taxing illness (eg, sepsis, pneumonia).

Spectrum of Fever and Fevers of Unknown Origin in Special Populations

Travel-Related Fever

Fever in returned travelers is most often due to malaria (47.6–75.2% of cases), followed by self-limited viral infections such as dengue virus (12.2%) and respiratory (3.4%) or urinary tract infections (1.4%) (Table 3) [34, 35]. Other infections such as gnathostomiasis, hepatitis A, hepatitis B, and hepatitis E infection, as well as rickettsial diseases, are occasionally diagnosed. Many exotic causes of fever typically fall short of the duration for FUO, including leptospirosis, schistosomiasis, or cysticercosis. Of the many febrile conditions encountered among returning travelers, geography should inform considerations. Often encountered illnesses that most frequently fit within an FUO definition among travelers include malaria, hepatitis A, typhoid fever, and acute HIV infection [34]. Clinicians should also consider noninfectious travel-related causes of FUO (eg, deep vein thrombosis, pulmonary embolism) to avoid inappropriately narrowing the differential diagnosis.

Nosocomial or Health Care–Associated Fever

Leading examples of causes attributable to nosocomial FUO include drug fever, postoperative complications (eg, occult abscesses), septic thrombophlebitis, recurrent pulmonary emboli, myocardial infarction/Dressler's syndrome, stroke, blood transfusion reactions, and *Clostridioides* (formerly *Clostridium*) *difficile* colitis [10, 36]. Among patients hospitalized with a recent stroke, fever is usually the result of an infection, most commonly a urinary tract infection related to urinary catheterization or respiratory tract infection. However, in a study of 330 patients hospitalized for acute stroke, Georgilis and associates [36] observed that noninfective fevers were most often

associated with intracranial hemorrhage-associated mass effects. These tended to occur earlier after the onset of stroke than fevers due to infection.

Although not all patients fit into a precise FUO definition, a more recent publication by Seguin and colleagues [37] investigated prolonged fevers (>5 days) among 507 hospitalized patients and reported that both infectious and noninfectious (eg, venous thrombosis, hematoma, pancreatitis, neurological) causes were found in 54 (62%) and 27 (31%) of 87 patients, respectively, with prolonged fever remaining unexplained in 6 (7%) patients. Intra-abdominal infections, ventilator-associated pneumonia, and vascular catheter-related infections were the most common infections. Risk factors for prolonged fever were cerebral injury at admission, severe sepsis, number of infections, and mechanical ventilation duration.

A prospective study by Kendrick and colleagues [38] looked at all patients (not just FUO) with postoperative fever among 292 patients admitted to a gynecologic oncology service after an abdominal or vaginal operation. In this group, 58 (20%) patients developed a postoperative fever. Among 37 (16%) low-risk surgical patients (eg, patients without bowel operation, preoperative infection, immunodeficiency, indwelling vascular access, mechanical heart valves, or intensive care unit admission) developing postoperative fevers, only 6 (3%) had an infection diagnosis. The majority of infections that did occur developed within 4 days of the operative procedure and included pneumonia, vaginal cuff cellulitis, and urinary tract infection. The authors proposed that postoperative fever is common and frequently represents the response to surgically induced tissue injury with the release of pyrogenic cytokines and interleukins rather than the result of infection. In another series concerned with the etiology of persistent postoperative fever in patients undergoing total joint arthroplasty, few definitive diagnoses were established, causing the authors also to conclude that postoperative fever (postoperative days 1 through 5) is a normal component of the inflammatory response to this type of major surgery [39].

Immunodeficiency-Associated Fever

In patients with impaired cell-mediated immunity or disrupted anatomic barriers arising from radiation or chemotherapy, FUO can be due to conditions other than pyogenic bacterial infections, as illustrated in a recent prospective evaluation of patients with leukemia and lymphoma by Toussaint and co-workers [40]. In that series, infections were the cause of 319 (67%) episodes of fever. The majority of infections included respiratory tract infections (28.8%), secondary bacteremia due to gram-negative bacilli (15.7%), genitourinary tract infections (12.9%), skin and soft tissue infections (11.3%), and primary bacteremia (11.0%). One hundred nine (23%) cases were due to noninfectious conditions such as malignant neoplasm, metastatic disease, and drug-induced fever. Although noninfectious neoplastic-related fever was more common (41%) among nonneutropenic patients, noninfectious drug-induced fever was more common among neutropenic patients (13%). In 47 (10%) cases, the cause of the fever could not be determined.

Most cases of FUO in HIV-infected patients are the result of opportunistic infections among patients not on highly active antiretroviral therapy (HAART) or with a suppressed viral load, the specific frequencies of which are dictated, at least in part, by geographic variation in the prevalence of these infections. In a report of 274 HIV-infected patients, for example, Abellan-Martinez and colleagues [41] observed an incidence range of 2.57 to 3.66 FUO episodes per 100 HIV-infected patients per year before the initiation of HAART and an incidence range of 0.84 to 1.24 events after the introduction of therapy. Because of the lack of well-established diagnostic criteria during the study period, immune reconstitution inflammatory syndrome (IRIS) was not reported as a cause of fever. In a recent study using 18-fluorodeoxyglucose–positron emission tomography/computed tomography (^{18}FDG-PET/CT) to investigate FUO reported by Martin and colleagues [42], the etiology of the FUO was identified in 17 of 20 (85%) patients. The causes of FUO in the patients for whom the etiology was determined included tuberculosis (n = 8), lymphoma (n = 3), nontuberculous mycobacteria (n = 3), pneumococcal infection (n = 1), visceral disseminated leishmaniasis (n = 1), and dental infection (n = 1). The remaining 3 patients had drug-induced or HIV-related fever.

Factitious or Prolonged Fevers

In their classic monograph, Petersdorf and Beeson [9] described the diagnosis of "factitious fever," in which 3 patients falsified temperature readings. Larson and colleagues (with Petersdorf) reported 3 patients with factitious fever in a series of 105 patients with classic FUO [18]. Many publications concerning the etiology of FUO have also described some factitious fever cases [17–30]. Patients are usually young women, aged 23–32, working in the medical profession (eg, nurse) with a prior history of psychiatric illnesses. The authors noted thermometer manipulation as the most common reason for documented fevers; however, this would be uncommon today, as electronic thermometer devices have replaced mercury instruments. Other maneuvers to fraudulently induce fever have included self-injection of microbes or pyrogenic substances (eg, toxins) [9, 18, 43].

Investigating 343 patients admitted to the National Institute of Allergy and Infectious Diseases, Aduan and colleagues [43] reported the largest number of patients (n = 32, 9%) with factitious fever. In this series, the majority of patients were female students or nurses (78%), with ages ranging from 15 to 38 years. The authors also noted fever durations ranging from 1 to 96 months. Psychiatric illnesses were only documented in 4 patients. Characteristics more likely to be associated

with factitious fever include markedly elevated temperatures (>41.1°C), 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's syndrome) [43].

Clinical, Laboratory, and Imaging Investigations

A deserving point to emphasize is that most patients in the original FUO description were not suffering from unusual or rare conditions; instead, they exhibited atypical manifestations of common illnesses in an era when diagnostic laboratory or imaging studies were more rudimentary [9, 17]. Over the nearly 60 years since, accumulated data from FUO studies not only include typical and atypical manifestations of common disorders but also rare conditions [9, 17–19, 30, 31, 33–35, 42, 44]. Changes to the original FUO definition by Durack and Street [10] stated that treatment is more time-critical for certain classes than others. Despite revised definitions and the introduction of improved serologic, laboratory, and imaging technologies, FUOs continue to elude diagnosis, suggesting that fevers may have many origins [44]. The most important lesson learned from the "classic FUO" concept is that, in many instances, available information from the history and physical examination should be utilized more often [9]. The literature is replete with algorithms indicating which laboratory tests should be performed to evaluate FUO [26, 44, 45]. Although useful as general guides, blind application of such algorithms may result in the performance of an excessive number of tests. They should be selectively applied using clues gleaned from the history, physical examination, laboratory studies, or imaging tests—also referred to as potentially diagnostic clues (PDCs) (Figure 2) [22, 26]. A PDC should help direct the choice and sequence of tests, possibly pointing toward a diagnosis (called Sutton's Law by Petersdorf and Beeson; recommends proceeding immediately to the diagnostic test most likely to provide a diagnosis rather carrying out a battery of "routine" sequential tests) [9].

Clinicians, though, need to be very well aware of the limitations with the "potential" aspect of any PDC. In a prospective study by De Kleijn and colleagues [22], of 167 patients meeting the criteria of classic FUO, PDCs led to a diagnosis in 101 patients (62%), which sounds promising. However, Bleeker-Rovers and colleagues [26] reported that an average of 15 PDCs were noted per patient, of which 19% contributed to the final diagnosis. A sobering 81% of PDCs were misleading in this series, a percentage that is substantially higher than that reported by De Kleijn and colleagues [22], in which as many as 48% of PDCs were misleading. Despite the poor outcomes of chasing clues, the authors soundly emphasize that the search for clues remains the most important clinical tool to unravel the cause of FUO.

Although imaging technologies such as CTs and magnetic resonance imaging (MRI) have greatly aided FUO evaluations, newer techniques such as ^{18}fluorodeoxyglucose–positron emitted tomography (^{18}FDG-PET) and MRI (diffusion-weighted images) have the potential to provide an opportunity to identify focal inflammatory or infectious processes before patients fulfill criteria for FUO or if traditional imaging studies were unrewarding [26, 42, 46, 47]. If looking at the broad array of imaging modalities for FUO, a more recent series reported sensitivities of 60% for plain-film chest radiograph, 82% for chest CT, 86% for abdominal ultrasound, and 92% for abdominal CT [26]. Older series did not have available PET scanning using the glucose analog ^{18}FDG, which highlights increased cellular glucose metabolism present in numerous hypermetabolic conditions, including tumors, focal areas of infection, and non-infectious inflammatory diseases.

However, ^{18}FDG PET and PET/CT have recently assumed an increasingly important role in the diagnostic workup of patients with FUO, with a reported sensitivity of 85%–86% [42, 46, 47]. It is especially useful for localizing lesions and areas of interest for further evaluation, such as biopsies. A recent meta-analysis reported that ^{18}FDG-PET and its combined modality with CT (^{18}FDG-PET/CT) successfully localized the source of fever in 58% of patients with classic FUO after a series of unsuccessful fever workup investigations [47]. In contrast to gallium and labeled leukocyte imaging, recent data indicate that ^{18}FDG contributes more diagnostically useful information than anatomic imaging like ultrasound and CT, which leads to the earlier institution of appropriate therapy [46, 47]. Additionally, standard ^{18}FDG-PET/CT protocols expose patients to less radiation (15 mSv) compared with conventional CT (20–25 mSv) and are not associated with nephrotoxicity [48].

A recent meta-analysis by Bharucha and colleagues [48] analyzed 18 retrospective observational case series of 905 patients to determine the diagnostic contribution of ^{18}FDG-PET/CT with FUO. Although the studies analyzed were associated with moderate to high heterogeneity ($I^2 > 50\%$), the authors reported an overall diagnostic contribution of 56% (95% confidence interval [CI], 50%–61%; $I^2 = 61\%$). A final diagnosis was made in 73% of cases (95% CI, 68%–78%), corresponding with 3 categories: 32% infectious diseases (95% CI, 27%–37%), 20% inflammatory diseases (95% CI, 17%–24%), and 12% malignancy (95% CI, 8%–17%). A point worth noting was that not all patients in these studies had undergone conventional imaging evaluation before obtaining an ^{18}FDG-PET/CT evaluation. In a subgroup analysis of 5 studies addressing the contribution of ^{18}FDG-PET/CT beyond patients receiving prior conventional imaging, the investigators reported a diagnostic yield of 32% (95% CI, 22%–44%; $I^2 = 66\%$). These findings suggest that ^{18}FDG-PET/CT imaging might be performed earlier, rather than later, in the diagnostic evaluation of patients with FUO. Practical issues in the United States may limit the utility of ^{18}FDG-PET imaging,

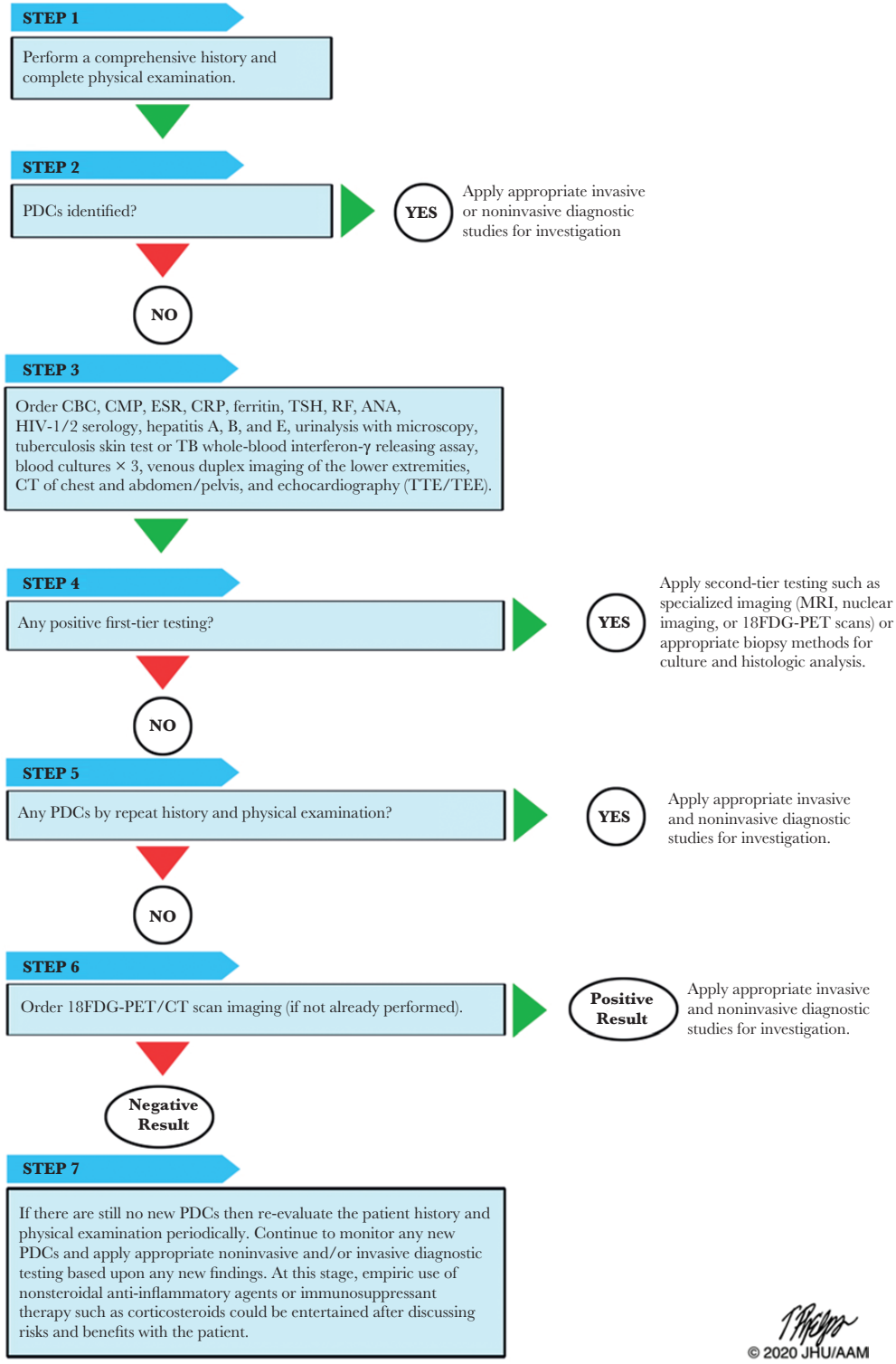

Figure 2. Suggested structured approach to investigating fever of unknown origin cases. This FUO algorithm is based upon limited data [26, 44, 45] and the authors' clinical opinion. Abbreviations: ^{18}FDG-PET, ^{18}fluorodeoxyglucose–positron emission tomography; ANA, antinuclear antibodies; CBC, complete blood count; CMP, comprehensive metabolic panel; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FUO, fever of unknown origin; MRI, magnetic resonance imaging; PDC, potential diagnosis clue; RF, rheumatoid factor; TEE, transesophageal echocardiogram; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram.

as not all hospital centers have this technology, and certain investigators, as well as health care insurers such the US Federal Government (Centers for Medicare and Medicaid Services), do not feel there has been sufficient prospective study proving its worth in FUO investigations and will deny payment for outpatient scans [49].

Patients in whom FUO remains undiagnosed after extensive noninvasive evaluation generally undergo more invasive procedures to establish an etiology. In a recent retrospective study of 100 patients continuously observed long term for classic FUO, Mete and colleagues [50] successfully identified specific etiologies in 61% of patients based on clinical features and noninvasive tests. Although invasive procedures (eg, laparotomy or biopsies) were performed in 79% of patients, a diagnostic benefit was obtained in only 49% of the cases. Biopsy procedures were the most common invasive procedure performed, yielding a diagnosis in 42%. Invasive procedures such as laparotomy, which were once considered a routine component of the FUO investigation, have now been replaced mainly by the development of advanced diagnostic imaging methods. The contribution of laparoscopy and laparotomy to the determination of FUO may now be most helpful in patients with solid cancer, peritoneal carcinomatosis, lymphoma, and disseminated tuberculosis [50].

Molecular diagnostic methods, whether singleplex or multiplex assays, have not yet become a frequently used tool in FUO investigations [26, 45, 51]. The few published peer-reviewed evaluations regarding the contribution of polymerase chain reaction (PCR) in patients with FUO have reported low yields, infrequently contributing to a final diagnosis [33, 52, 53]. Application of PCR among a Greek cohort being evaluated for suspected extrapulmonary *M. tuberculosis* also yielded low and variable contributions to the final diagnosis, ranging from 22.3% to 41.6% [54, 55]. The value of PCR was more useful among patients with PDCs present and negative cultures [54]. Though techniques such as 16s ribosomal analysis have yielded diagnoses of fastidious organisms such as *Tropheryma whippelii,* the agent of Whipple's disease, whether this assay or newer methods such as next-generation sequencing should be routinely used in FUO will require larger studies to understand their accuracy and utility [56].

Management and Prognosis

A fundamental principle in the management of FUO is that empirical antimicrobial therapy should be withheld whenever possible in a stable non-neutropenic or immunocompromised and/or non–critically ill patient until the cause of the fever has been determined so that that treatment can be tailored to a specific diagnosis [9, 10]. This approach is based on the oft-repeated observation that nonspecific treatment rarely cures FUO and has the potential to delay reaching the correct diagnosis [57, 58]. In contrast, for the critically ill and/or febrile neutropenic or immunocompromised patient, the principles of empirical antimicrobial treatment are entirely different [59]. Because of the relatively high prevalence of serious bacterial or invasive fungal infections responsible for these fevers, febrile neutropenic patients should generally receive broad-spectrum antimicrobial therapy immediately after samples for appropriate cultures have been obtained [59].

Although the prognosis of FUO is determined by the cause of that fever and by the nature of any underlying disease or diseases, most patients with prolonged undiagnosed FUO have a favorable outcome. In older series, a mortality rate of 12%–35% has been reported for diseases underlying classic FUO [9, 18]. In a series of 91 patients undergoing evaluation for FUO, Mansueto and colleagues [28] 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 died as a result of noninfectious complications considered to be 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 disproportionally higher fatality rate (60%) among patients with non-Hodgkin lymphoma. Fatality rates were <6%, among other categories.

Spontaneous resolution, with or without an eventual diagnosis, has been reported in as many as 75% of FUO patients [22, 26, 58]. Studies of FUO resolution have only enrolled patients over the age of 18 years [22, 24, 26, 61]. How frequently this occurs in pediatric FUO is not well described, nor are comparisons with adults. Bleeker-Rovers and colleagues [24] reported spontaneous resolution of fever 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 meta-analysis of 13 retrospective studies, Takeuchi and colleagues [61] reported an average spontaneous remission rate of 20% (range, 6%–45%). Among 418 patients with a negative ^{18}FDG-PET/CT, the incidence of spontaneous fever remission ranged from 20% to 78%. The average proportion of FUO causes were 31% infections, 25% inflammatory diseases, 14% malignancies, and 3% miscellaneous. The investigators concluded that patients have a higher probability of spontaneous fever resolution and favorable prognosis with a negative ^{18}FDG-PET/CT compared with those with a positive abnormal finding.

CONCLUSIONS

Despite lingering perceptions, 37.0°C (98.6°F) is rooted in a historical convention that modern data argue should not continue to be regarded as normal average body temperature. Sensitivity for the detection of illness may be inappropriately lowered if 38.0°C and 38.3°C continue to be the standards. Yet adoption of a lower normal temperature value, or normal temperature range, will likely require a high-profile effort such as a National Academy of Science–sponsored study to redefine one of the most critical and ubiquitous measures in clinical medicine.

FUO remains a challenging clinical condition. The heterogeneity of the disorder, the lack of multicentered, high-quality studies, and the extensive breadth of possible diagnostic techniques mean that clinical judgment remains an essential component of care. Advancements such as ^{18}FDG-PET/CT appear to offer clinicians a helping hand in the more difficult FUO cases; however, studies examining its use are limited and, unfortunately, not convincing enough to establish a clear-cut role from some perspectives, such as those of insurance companies.

Unlike Petersdorf and Beeson's era when most cases seemed restricted to a few diseases, primarily infections, the differential diagnosis of FUO has grown to include many new causes [44] as science has evolved; this investigation must be the longest of any in medicine. A meticulous history, thorough physical examination, discriminating use of investigative procedures, and constant reevaluation of the clinical evidence will usually reveal the etiology. Knowing that many cases of FUO might be atypical manifestations of common diseases and how to appropriately apply available diagnostic tools is the diagnostician's good friend, and when careful, patient observation is better than further blind investigative or therapeutic investigations involving classic FUO cases. For the many patients who remain without a diagnosis despite extensive evaluations, there is some reassuring news that, for many, the fevers will remit without serious complications. Despite all the medical advances since the report by Petersdorf and Beeson in 1961 [9], the art of medicine is perhaps not better appreciated anywhere more than as a core principle in the FUO diagnosis.

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References

1. Sajadi MM, Bonabi R, Sajadi MR, Mackowiak PA. Akhawayni and the first fever curve. Clin Infect Dis **2012**; 55:976–80.
2. Wright WF, Mackowiak PA. Origin, evolution and clinical application of the thermometer. Am J Med Sci **2016**; 351:526–34.
3. Mackowiak PA, Worden G. Carl Reinhold August Wunderlich and the evolution of clinical thermometry. Clin Infect Dis **1994**; 18:458–67.
4. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. JAMA **1992**; 268:1578–80.
5. Dominguez EA, Bar-Sela A, Musher DM. Adoption of thermometry into clinical practice in the United States. Rev Infect Dis **1987**; 9:1193–201.
6. Geneva II, Cuzzo B, Fazili T, Javaid W. Normal body temperature: a systematic review. Open Forum Infect Dis **2019**; 6:XXX–XX.
7. Adhi M, Hasan R, Noman F, et al. Range for normal body temperature in the general population of Pakistan. J Pak Med Assoc **2008**; 58:580–4.
8. Protsiv M, Ley C, Lankester J, et al. Decreasing human body temperature in the United States since the industrial revolution. Elife **2020**; 9:e49555.
9. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) **1961**; 40:1–30.
10. Durack DT, Street AC. Fever of unknown origin—reexamined and redefined. Curr Clin Top Infect Dis **1991**; 11:35–51.
11. Mackowiak PA. Concepts of fever. Arch Intern Med **1998**; 158:1870–81.
12. Kobayashi S. Temperature receptors in cutaneous nerve endings are thermostat molecules that induce thermoregulatory behaviors against thermal load. Temperature (Austin) **2015**; 2:346–51.
13. Romanovsky AA. Skin temperature: its role in thermoregulation. Acta Physiol (Oxf) **2014**; 210:498–507.
14. Mackowiak PA, Boulant JA. Fever's glass ceiling. Clin Infect Dis **1996**; 22:525–36.
15. Roth J, Blatteis CM. Mechanisms of fever production and lysis: lessons from experimental LPS fever. Compr Physiol **2014**; 4:1563–604.
16. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. Nat Rev Immunol **2015**; 15:335–49.
17. Petersdorf RG, Larson E. FUO revisited. Trans Am Clin Climatol Assoc **1983**; 94:44–54.
18. Larson EB, Featherstone HJ, Petersdorf RG. Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970-1980. Medicine (Baltimore) **1982**; 61:269–92.
19. Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s. An update of the diagnostic spectrum. Arch Intern Med **1992**; 152:51–5.
20. Barbado FJ, Vázquez JJ, Peña JM, et al. Pyrexia of unknown origin: changing spectrum of diseases in two consecutive series. Postgrad Med J **1992**; 68:884–7.
21. Kazanjian PH. Fever of unknown origin: review of 86 patients treated in community hospitals. Clin Infect Dis **1992**; 15:968–73.
22. De Kleijn EMHA, Vandenbroucke JP, van der Meer JWM, et al. Fever of unknown origin (FUO), I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. Medicine **1997**; 76:392–400.
23. Vanderschueren S, Knockaert D, Adriaenssens T, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. Arch Intern Med **2003**; 163:1033–41.
24. Saltoglu N, Tasova Y, Midikli D, et al. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. J Infect **2004**; 48:81–5.
25. Ergönül O, Willke A, Azap A, Tekeli E. Revised definition of 'fever of unknown origin': limitations and opportunities. J Infect **2005**; 50:1–5.
26. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine (Baltimore) **2007**; 86:26–38.
27. Colpan A, Onguru P, Erbay A, et al. Fever of unknown origin: analysis of 71 consecutive cases. Am J Med Sci **2007**; 334:92–6.
28. Mansueto P, Di Lorenzo G, Rizzo M, et al. Fever of unknown origin in a Mediterranean survey from a division of internal medicine: report of 91 cases during a 12-year-period (1991-2002). Intern Emerg Med **2008**; 3:219–25.
29. Bandyopadhyay D, Bandyopadhyay R, Paul R, et al. Etiologic study of fever of unknown origin in patients admitted to medicine ward of a teaching hospital of Eastern India. J Glob Infect Dis **2011**; 3:329–33.
30. Naito T, Tanei M, Ikeda N, et al. Key diagnostic characteristics of fever of unknown origin in Japanese patients: a prospective multicentre study. BMJ Open **2019**; 9:e032059.
31. Fusco FM, Pisapia R, Nardiello S, et al. Fever of unknown origin (FUO): which are the factors influencing the final diagnosis? A 2005-2015 systematic review. BMC Infect Dis **2019**; 19:653.
32. Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. World J Pediatr **2011**; 7:5–10.
33. Zhou W, Tan X, Li Y, Tan W. Human herpes viruses are associated with classic fever of unknown origin (FUO) in Beijing patients. PLoS One **2014**; 9:e101619.
34. Antinori S, Galimberti L, Gianelli E, et al. Prospective observational study of fever in hospitalized returning travelers and migrants from tropical areas, 1997-2001. J Travel Med **2004**; 11:135–42.
35. Parola P, Soula G, Gazin P, et al. Fever in travelers returning from tropical areas: prospective observational study of 613 cases hospitalised in Marseilles, France, 1999-2003. Travel Med Infect Dis **2006**; 4:61–70.
36. Georgilis K, Plomaritoglou A, Dafni U, et al. Aetiology of fever in patients with acute stroke. J Intern Med **1999**; 246:203–9.
37. Seguin P, Roquilly A, Mimoz O, et al; AtlanRea Group. Risk factors and outcomes for prolonged versus brief fever: a prospective cohort study. Crit Care **2012**; 16:R150.
38. Kendrick JE, Numnum TM, Estes JM, et al. Conservative management of postoperative fever in gynecologic patients undergoing major abdominal or vaginal operations. J Am Coll Surg **2008**; 207:393–7.
39. Shaw JA, Chung R. Febrile response after knee and hip arthroplasty. Clin Orthop Relat Res **1999**; 367:181–9.

40. Toussaint E, Bahel-Ball E, Vekemans M, et al. Causes of fever in cancer patients (prospective study over 477 episodes). Support Care Cancer **2006**; 14:763–9.
41. Abellán-Martínez J, Guerra-Vales JM, Fernández-Cotarelo MJ, González-Alegre MT. Evolution of the incidence and aetiology of fever of unknown origin (FUO), and survival in HIV-infected patients after HAART (highly active antiretroviral therapy). Eur J Intern Med **2009**; 20:474–7.
42. Martin C, Castaigne C, Tondeur M, et al. Role and interpretation of fluorodeoxyglucose-positron emission tomography/computed tomography in HIV-infected patients with fever of unknown origin: a prospective study. HIV Med **2013**; 14:455–62.
43. Aduan RP, Fauci AS, Dale DC, et al. Factitious fever and self-induced infection: a report of 32 cases and review of the literature. Ann Intern Med **1979**; 90:230–42.
44. Horowitz HW. Fever of unknown origin or fever of too many origins? N Engl J Med **2013**; 368:197–9.
45. de Kleijn EM, van Lier HJ, van der Meer JW. Fever of unknown origin (FUO). II. Diagnostic procedures in a prospective multicenter study of 167 patients. The Netherlands FUO Study Group. Medicine (Baltimore) **1997**; 76:401–14.
46. Dong MJ, Zhao K, Liu ZF, et al. A meta-analysis of the value of fluorodeoxyglucose-PET/PET-CT in the evaluation of fever of unknown origin. Eur J Radiol **2011**; 80:834–44.
47. Takeuchi M, Dahabreh IJ, Nihashi T, et al. Nuclear imaging for classic fever of unknown origin: meta-analysis. J Nucl Med **2016**; 57:1913–9.
48. Bharucha T, Rutherford A, Skeoch S, et al. Diagnostic yield of FDG-PET/CT in fever of unknown origin: a systematic review, meta-analysis, and Delphi exercise. Clin Radiol **2017**; 72(9):764–771.
49. Censullo A, Vijayan T. Using nuclear medicine imaging wisely in diagnosing infectious diseases. Open Forum Infect Dis **2017**; 4:XXX–XX.
50. Mete B, Vanli E, Yemisen M, et al. The role of invasive and non-invasive procedures in diagnosing fever of unknown origin. Int J Med Sci **2012**; 9:682–9.
51. Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med **2003**; 163:545–51.
52. Persson L, Dahl H, Linde A, et al. Human cytomegalovirus, human herpesvirus-6 and human herpesvirus-7 in neutropenic patients with fever of unknown origin. Clin Microbiol Infect **2003**; 9:640–4.
53. Krumova S, Pavlova A, Yotovska K, et al. Combined laboratory approach to detection of parvovirus B19 and *Coxiella burnetii* in patients with fever of unknown origin. Clin Lab. **In press**.
54. Ritis K, Tzoanopoulos D, Speletas M, et al. Amplification of IS6110 sequence for detection of *Mycobacterium tuberculosis* complex in HIV-negative patients with fever of unknown origin (FUO) and evidence of extrapulmonary disease. J Intern Med **2000**; 248:415–24.
55. Singh UB, Bhanu NV, Suresh VN, et al. Utility of polymerase chain reaction in diagnosis of tuberculosis from samples of bone marrow aspirate. Am J Trop Med Hyg **2006**; 75:960–3.
56. Pron B, Poyart C, Abachin E, et al. Diagnosis and follow-up of Whipple's disease by amplification of the 16S rRNA gene of *Tropheryma whippelii*. Eur J Clin Microbiol Infect Dis **1999**; 18:62–5.
57. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc **2011**; 86:156–67.
58. Mulders-Manders CM, Engwerda C, Simon A, et al. Long-term prognosis, treatment, and outcome of patients with fever of unknown origin in whom no diagnosis was made despite extensive investigation: a questionnaire based study. Medicine (Baltimore) **2018**; 97:e11241.
59. Freifeld AG, Bow EJ, Sepkowitz KA, et al; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis **2011**; 52:e56–93.
60. Vanderschueren S, Eyckmans T, De Munter P, Knockaert D. Mortality in patients presenting with fever of unknown origin. Acta Clin Belg **2014**; 69:12–6.
61. Takeuchi M, Nihashi T, Gafter-Gvili A, et al. Association of 18F-FDG PET or PET/CT results with spontaneous remission in classic fever of unknown origin: a systematic review and meta-analysis. Medicine (Baltimore) **2018**; 97:e12909.