> ## REVIEW ARTICLE

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Fever of Unknown Origin

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PERSISTENT FEVER WITH AN ELUSIVE CAUSE HAS BEEN RECOGNIZED FOR more than a century. In 1907, Cabot, a cofounder of the Clinicopathological Conferences at Massachusetts General Hospital, characterized fever lasting for 2 weeks or longer as "long fever."[1] Over the ensuing decades, many studies of unexplained fever have been conducted with the use of various diagnostic criteria. In 1961, Petersdorf and Beeson defined fever of unknown origin (FUO) as a temperature of 38.3°C or higher for at least 3 weeks without a diagnosis, despite 1 week of inpatient investigations.[2] With the evolution of health care delivery in the ambulatory setting, Durack and Street's revised criteria shortened the investigation period to 3 inpatient days or at least 3 outpatient visits.[3]

FUO is not a biologically uniform phenomenon but rather a common manifestation of multiple, disparate disease processes. There are different classifications for FUO that are based on the immune status of the host, whether the patient is hospitalized, and travel history. It is therefore not surprising that the temperature, duration, and workup criteria for FUO have evolved over the past century.[4] These newer definitions have generally relied on a composite of time-based and minimally diagnostic criteria.[4-6] However, there is no universal agreement on the precise time cutoff or diagnostic criteria for FUO. For instance, two prospective studies from the Netherlands defined FUO as a temperature exceeding 38.3°C and lasting for more than 3 weeks despite a negative extensive workup,[5,6] with an acknowledgment that a reasonable approach to reducing bias in FUO cases may be to abandon time-based criteria, which may vary by country of origin, in favor of a list of negative investigations (for which there is no consensus). Indeed, in a systematic review of FUO, 28% of the studies defined FUO as fever after a nonrevealing minimal diagnostic workup, without the use of rigid time-dependent criteria.[7] However, there continues to be value in incorporating the duration of fever in the definition of FUO, in order to avoid using the term for self-limited febrile conditions. Because of the heterogeneous nature of FUO, whether the specified duration should be 2 weeks, 3 weeks, or another length of time is a matter of both debate and expert opinion.[4]

Thus, although any proposed definition of FUO is subjective, the core features are the absence of an identified cause of fever, despite reasonable investigations in either the inpatient or outpatient setting, and the persistence of fever for a sufficient time to rule out self-limiting fevers.[6,8] Clinicians caring for febrile patients should be cognizant of these controversies, complexities, and nuances and should approach the patient with possible FUO not through the lens of rigid and arbitrary algorithms but rather through a thoughtful and critical appraisal of how long the patient has been febrile and whether a thorough set of investigations has been performed. The latter evaluation refers to "quality-based" criteria that require a list of certain investigations to be performed, many of which are prompted by potential diagnostic clues. Although the specific investigations conducted before a diagnosis of FUO can be established are debatable,[8] a minimal workup should
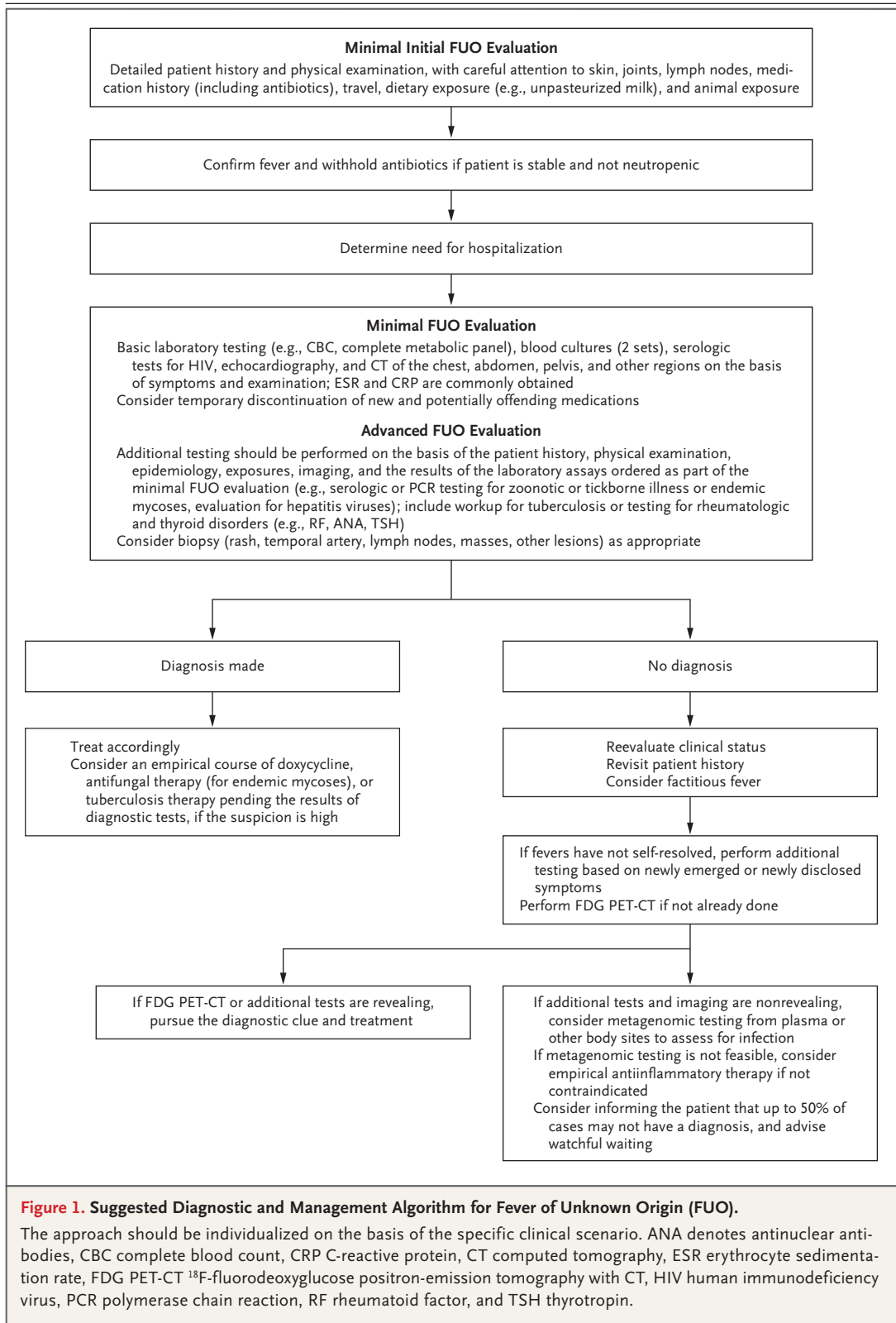
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Minimal Initial FUO Evaluation

Detailed patient history and physical examination, with careful attention to skin, joints, lymph nodes, medication history (including antibiotics), travel, dietary exposure (e.g., unpasteurized milk), and animal exposure

Confirm fever and withhold antibiotics if patient is stable and not neutropenic

Determine need for hospitalization

Minimal FUO Evaluation

Basic laboratory testing (e.g., CBC, complete metabolic panel), blood cultures (2 sets), serologic tests for HIV, echocardiography, and CT of the chest, abdomen, pelvis, and other regions on the basis of symptoms and examination; ESR and CRP are commonly obtained
Consider temporary discontinuation of new and potentially offending medications

Advanced FUO Evaluation

Additional testing should be performed on the basis of the patient history, physical examination, epidemiology, exposures, imaging, and the results of the laboratory assays ordered as part of the minimal FUO evaluation (e.g., serologic or PCR testing for zoonotic or tickborne illness or endemic mycoses, evaluation for hepatitis viruses); include workup for tuberculosis or testing for rheumatologic and thyroid disorders (e.g., RF, ANA, TSH)
Consider biopsy (rash, temporal artery, lymph nodes, masses, other lesions) as appropriate

Diagnosis made

No diagnosis

Treat accordingly
Consider an empirical course of doxycycline, antifungal therapy (for endemic mycoses), or tuberculosis therapy pending the results of diagnostic tests, if the suspicion is high

Reevaluate clinical status
Revisit patient history
Consider factitious fever

If fevers have not self-resolved, perform additional testing based on newly emerged or newly disclosed symptoms
Perform FDG PET-CT if not already done

If FDG PET-CT or additional tests are revealing, pursue the diagnostic clue and treatment

If additional tests and imaging are nonrevealing, consider metagenomic testing from plasma or other body sites to assess for infection
If metagenomic testing is not feasible, consider empirical antiinflammatory therapy if not contraindicated
Consider informing the patient that up to 50% of cases may not have a diagnosis, and advise watchful waiting

Figure 1. Suggested Diagnostic and Management Algorithm for Fever of Unknown Origin (FUO).

The approach should be individualized on the basis of the specific clinical scenario. ANA denotes antinuclear antibodies, CBC complete blood count, CRP C-reactive protein, CT computed tomography, ESR erythrocyte sedimentation rate, FDG PET-CT ^{18}F-fluorodeoxyglucose positron-emission tomography with CT, HIV human immunodeficiency virus, PCR polymerase chain reaction, RF rheumatoid factor, and TSH thyrotropin.

generally be undertaken before a patient is considered to have FUO (Fig. 1), with the understanding that the specific testing performed may vary on the basis of epidemiologic, host, resource-related, and other factors. It is also understood that testing may be performed not simultaneously but rather sequentially as diagnoses are ruled in or out.

THE FEBRILE RESPONSE

Thermometry did not become mainstream until Wunderlich's pioneering work on temperature in 1868.[9] Using a foot-long instrument that took 20 minutes to register, he recorded more than a million axillary readings and established normal body temperature as 37.0°C (98.6°F). Since the 19th century, however, human bodies appear to have gradually become colder.[10] New population-based data show that body temperatures have been steadily declining at a rate of approximately 0.03 to 0.5°C per decade; currently, the normal range is 36.3 to 36.5°C.[10] Inflammatory, environmental, and other changes during the previous two centuries are among the proposed reasons for these observations.[10]

The preoptic area and anterior hypothalamus play key roles in thermal homeostasis. Induction of pyrogenic cytokines (e.g., interleukin-1 and interleukin-6) by pathogens or inflammatory stimuli triggers prostaglandin E_2 production by brain endothelial cells, which resets the thermoregulatory set point in the preoptic area and thus elicits a febrile response.[11] The preoptic area also controls other thermoregulatory responses, including cutaneous vasoconstriction, nonshivering thermogenesis in brown adipose tissue, and shivering thermogenesis in skeletal muscles. Fever-related anorexia is also prostaglandin-mediated. Whereas pyrogens induce fever, counterregulatory cytokines (e.g., interleukin-10) and other endogenous antipyretic mediators function as cryogens (inhibitors of fever) and prevent detrimental elevations of temperature.[11]

SEQUELAE OF FEVER

Perspectives regarding the effect of fever on disease outcomes have evolved over millennia.[12] Ancient scholars considered febrile responses to be beneficial.[12] Since the early 19th century, fever has widely come to be perceived as harmful.[12] However, phylogenetic conservation of fever for millions of years in the animal kingdom suggests that it is potentially beneficial to the host. Most pathogenic bacteria are mesophiles (i.e., organisms for which a temperature of approximately 35°C is ideal for their growth), and febrile-range temperatures inhibit their proliferation.[13] Fever also generates hepatic iron-sequestering compounds that bind the free iron necessary for microbial replication, augments the antimicrobial activity of antibiotic agents, induces heat-sensitive shock proteins that activate host defenses, and enhances T-cell responses.[14,15] One study showed that temperatures up to 39.5°C in critically ill patients had no adverse effects and may have even been associated with favorable outcomes.[16] Warming by external means, however, is not beneficial.

TEMPORAL CHANGES IN THE CAUSES OF FUO

Large shifts in the causes of FUO have occurred during the past century.[2,17] An overall perception in the literature is that as compared with the early 1900s and mid-1900s, the current era has witnessed a reduction in infectious causes of FUO, with a rise in autoimmune or autoinflammatory conditions.[2,17] However, a closer appraisal of studies reveals a more complex picture in which the causes of FUO vary depending on the country, type of hospital (tertiary vs. community), and patient population. The literature is contradictory and refutes the prevailing perception that inflammatory conditions have surpassed infections as the predominant cause of FUO, with two systematic reviews, from 1994 to 2004[17] and from 2005 to 2015,[7] showing that infections remain the leading causes of FUO. There appears to be a possible association between lower-income regions and a higher prevalence of infection.[7] For instance, in India[18] and Turkey[19] in 2021, infections accounted for approximately 40% of cases of FUO, whereas autoimmune and inflammatory conditions accounted for only a quarter of cases. In contrast, contemporaneous studies from Japan,[20] Greece,[21] and South Korea[22] have shown either an equal proportion or a greater frequency of autoimmune and inflammatory conditions. Up to 51% of cases of FUO, even in the current

Table 1. Broad Categories of Fever of Unknown Origin (FUO).*

Category	Definition and Causes
Classic FUO	FUO despite reasonable initial investigations in the inpatient or outpatient setting; includes FUO in persons with HIV infection who are virally suppressed, with CD4 counts >200 cells/mm³; causes fall into four categories: infections (e.g., tuberculosis, endocarditis, occult abscesses, Whipple's disease, enteric fever, syphilis [mainly secondary], various zoonoses, and histoplasmosis), cancer, autoimmune and autoinflammatory disorders, and miscellaneous causes
Nosocomial FUO	FUO that develops in hospitalized persons
ICU patients	Causes include infections (bacteremia, pneumonia, *Clostridioides difficile* infection, fungemia, catheter-associated infections, decubitus ulcers), thromboembolic events, acalculous cholecystitis, drug-associated fever, strokes, cerebral hemorrhages, and bleeding
Non-ICU patients	Similar causes to those listed for FUO in ICU setting, although patients are not critically ill
Immunodeficiency-associated FUO	Causes are highly variable, depending on the type of underlying immunodeficiency
Organ-transplant recipients	Causes include viruses, donor-derived infections, *Strongyloides stercoralis* hyperinfection, opportunistic fungal infections, rejection, and in rare cases, GVHD, graft intolerance syndrome (from retained kidney grafts in situ after graft failure), old nonfunctioning arteriovenous grafts after kidney transplantation (may cause occult infection or fever), hemophagocytic lymphohistiocytosis, and ureaplasma-related hyperammonemia syndrome
Patients with neutropenia	High-risk patients with neutropenia are considered to have FUO if they have been febrile for >5 days despite appropriate empirical antibiotic therapy; etiologic diagnosis affected by duration of neutropenia, immunosuppression for GVHD treatment or prophylaxis, and prophylactic antimicrobial therapy
Hematopoietic-cell transplant recipients	Causes before engraftment: similar to causes of neutropenic FUO Causes in early period after engraftment: engraftment itself, opportunistic herpesvirus infections, adenovirus infection, hyperacute GVHD, infectious pneumonia, idiopathic pneumonia syndrome Causes in late period after engraftment: multiple causes, including relapsed cancer; immune reconstitution is not fully restored for approximately 24 mo, and patients remain at risk for infection (e.g., from encapsulated organisms) during that period
Patients with HIV infection not receiving ART, patients with AIDS	Causes include acute retroviral syndrome, mycobacterial infection, endemic mycoses, toxoplasmosis, cryptococcosis, HHV-8 infection (e.g., Kaposi's sarcoma, primary effusion lymphoma, Kaposi's sarcoma herpesvirus inflammatory cytokine syndrome), and lymphoma
Travel-associated FUO	Causes include malaria, enteric fever, leptospirosis, viral hemorrhagic fevers, typhus, and acute undifferentiated febrile illness of tropical countries[24]

* The table includes a selected list of entities that may be associated with FUO. Data are from Durack and Street[3] and Wright and Auwaerter.[23] AIDS denotes acquired immunodeficiency syndrome, ART antiretroviral therapy, GVHD graft-versus-host disease, HHV human herpesvirus, HIV human immunodeficiency virus, and ICU intensive care unit.

era, remain undiagnosed.[5] The likelihood of undiagnosed cases may be greater in higher-income regions, an association that is probably due to overrepresentation of patients with "difficult to diagnose" conditions.[7]

FUO CLASSIFICATION

Historically, FUO has been divided into classic, nosocomial, immunodeficiency-related, and travel-associated cases (Table 1). Despite its limitations, such a classification provides a useful framework with which to approach the patient with prolonged fever.

CLASSIC FUO

The term "classic FUO" typically refers to variations of the FUO syndrome that was initially defined by Petersdorf and Beeson[23] and has been the focus of most FUO-related reports over the past century. The major causes of classic FUO are infections, cancers, autoinflammatory or autoimmune conditions, and miscellaneous causes.[3] A review of all infections causing FUO is not possible here; however, the following key entities warrant discussion.

Bacterial Infections

Tuberculosis has been among the most common infectious causes of FUO. Tuberculosis was diagnosed in at least one patient in 32 of 35 studies of FUO and was more common in non-U.S. series (10.2%) than in U.S. series (5.3%).[25] The diagnosis of miliary, or disseminated, tuberculosis remains challenging, given its protean manifestations, frequent absence of antecedent tuberculosis,
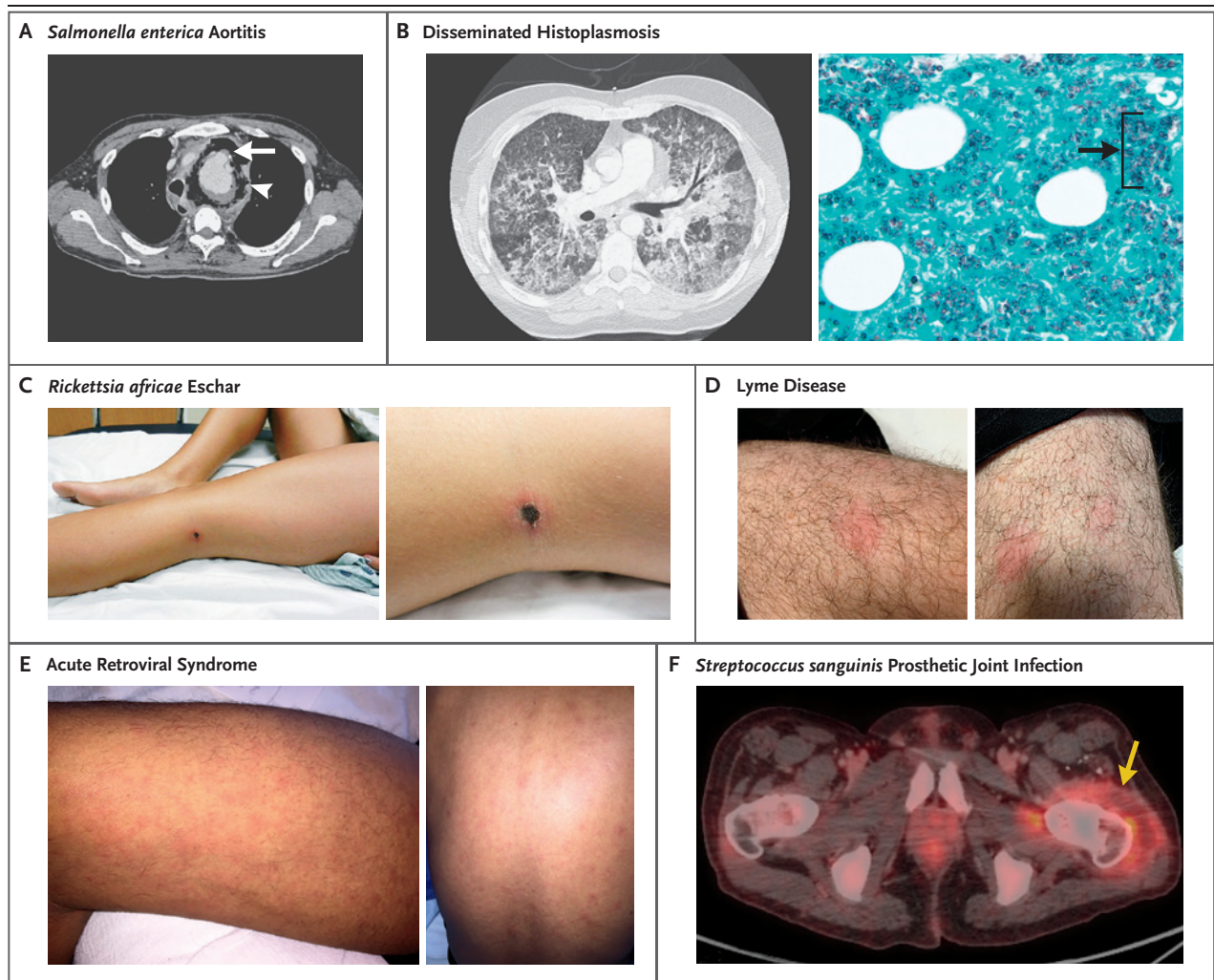
Figure 2. Selected Examples of FUO Cases Caused by Infections.

Panel A shows a pseudoaneurysm in the aortic arch (arrow) with extensive gas collection (arrowhead), indicating *Salmonella enterica* aortitis, in a patient with fever for 1 month.[26] Panel B shows a chest CT scan and a smear of bone marrow aspirate from a patient with hilar lymphadenopathy and noncaseating granulomas who received glucocorticoids for presumed sarcoidosis. Bronchoalveolar-lavage fluid and bone marrow aspirate obtained on a subsequent admission grew *Histoplasma capsulatum*; serum and urinary tests for histoplasma antigens were positive. Repeated review of the initial pathological slide of bone marrow aspirate, with Grocott methenamine–silver staining, revealed many histoplasma yeasts (arrow). Panel C shows an inoculation eschar in a patient with fever, headache, and myalgia after a hunting trip to South Africa. A PCR assay of a punch-biopsy sample of the eschar yielded *Rickettsia africae*.[27] Panel D shows early, disseminated Lyme disease in a man with fever and rash. Panel E shows rash in a patient with HIV and an acute retroviral syndrome. Panel F shows an FDG PET-CT scan of a hip prosthesis in a patient who had Crohn's disease with fevers, sweats, and weight loss over a period of approximately 6 months. Trials of glucocorticoids, antibiotics, and antifungal agents had failed. On repeated review of the FDG PET-CT scan, a fluid collection in the hip prosthesis (arrow) was noted, with cultures yielding *Streptococcus sanguinis*. Surgery and treatment with ceftriaxone led to complete recovery.

unremarkable chest radiographs, and inadequate diagnostic tools. Approximately 38% of patients with Whipple's disease present with fever, often with arthralgia or arthritis, diarrhea, and weight loss. Typhoidal and nontyphoidal salmonella serovars can cause bacteremia and FUO and can be complicated by mycotic aneurysms (Fig. 2A). Other bacterial infections (e.g., infective endocarditis, particularly culture-negative endocarditis) and deep-seated infections (e.g., abscesses and prostatitis) remain time-honored entities associated with FUO.[6]

Viral Infections

Although most viral infections are self-limited, establishing a diagnosis may curtail diagnostic testing costs and antibiotic use. In a study from China, human herpesviruses were detected with a plasma polymerase-chain-reaction (PCR) assay in one third of patients with FUO and included cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpesvirus 6 (HHV-6), and HHV-7 in 15.1%, 9.7%, 14.0%, and 4.8% of patients, respectively, with coinfections present in 10.2% of patients.[28] Fevers occurred either alone or with elevated aminotransferase levels or hematologic abnormalities; fever with hematologic abnormalities was most common with EBV viremia. However, many instances of herpesvirus replication represent reactivation of latent infection in the context of another process, as opposed to being the primary cause of FUO. The clinical presentation of infectious mononucleosis may vary with age (e.g., middle-aged or elderly persons are likely to have a longer duration of fever and more pronounced leukopenia but a lower incidence of splenomegaly, pharyngitis, and lymphadenopathy than adolescents).[29] Mononucleosis should therefore be considered in patients with FUO, regardless of age. HHV-6 and HHV-8 should generally be tested only in immunocompromised patients; the pathogenicity of HHV-7 is debatable.[30] Zoonotic viruses are a consideration in FUO, particularly when accompanied by meningoencephalitis (Table 2, and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Fungal Infections

The endemic mycoses (histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis) may be associated with FUO in both immunocompetent and immunocompromised hosts, with the exception of talaromycosis, which primarily affects immunocompromised persons (Table S2).[32] In contrast, the opportunistic invasive mycoses, such as aspergillosis, mucormycosis, and cryptococcosis due to *Cryptococcus neoformans* (but not due to *C. gattii*, which can infect healthy persons), occur largely in immunocompromised persons. Endemic mycoses have overlapping and nonspecific clinical manifestations, including B symptoms and pulmonary or extrapulmonary symptoms. A travel history may assist in establishing the diagnosis. However, areas in which mycoses are endemic can shift over time. Indeed, despite decades of dogma, it is apparent that the distribution of histoplasmosis is expanding beyond the Mississippi and Ohio River Valleys.[33] Thus, histoplasmosis should be suspected in patients with compatible syndromes (Fig. 2B), even outside the classic histoplasma map, which was first published in 1969 on the basis of skin testing conducted between 1958 and 1965.[33] Unfortunately, many cases of histoplasmosis continue to be diagnosed on the basis of tissue biopsies rather than antigen testing, suggesting that the index of suspicion among providers remains low.[33]

Other Infections

Approximately one half of human pathogens are vectorborne or zoonotic,[34] and these infections are often manifested as FUO (Table 2, Fig. 2C and 2D, Table S1).[35] A clear history of zoonotic or arthropod exposure is typically absent. In addition, the overlapping and nonspecific clinical manifestations, which may include rash, cytopenia, and elevated aminotransferase levels, and the lack of readily available laboratory testing often result in diagnostic delays.

Cancers

Cancers constitute approximately 2 to 25% of cases of FUO.[2,3,36] Neoplasms most frequently associated with FUO include renal-cell carcinoma, lymphomas, hepatocellular and ovarian cancer, atrial myxoma, and Castleman's disease[37] (Table 3). Pyrogenic cytokine production or spontaneous tumor necrosis (with or without secondary infections) is the likely basis of most cancer-related fever.[23] The "naproxen challenge" has been proposed to differentiate FUO due to cancers from FUO due to infections.[40] Although clinicians may choose to use naproxen for symptomatic relief of fevers, amelioration or resolution of fevers with naproxen does not obviate the need for a rigorous evaluation for infection.

Autoinflammatory and Autoimmune Disorders

Autoinflammatory and autoimmune diseases account for 5 to 32% of FUO cases.[2,7,17,19] Emerging mechanistic knowledge of these disorders has shown that the two entities are distinct. Purely autoinflammatory conditions (e.g., periodic fever syndromes) are disorders of innate immunity with dysregulated interleukin-1β responses, in-

terleukin-18 responses, or both, whereas autoimmune diseases (e.g., autoimmune lymphoproliferative syndrome) involve adaptive immunity and are driven by a type 1 interferon response.[39] Other disorders (e.g., adult-onset Still's disease and rheumatoid arthritis) have variable or concurrent autoinflammatory and autoimmune components[39] (Table 3). Giant-cell arteritis and polymyalgia rheumatica in the elderly and adult-onset Still's disease in younger patients are commonly associated with fever. Elevated inflammatory markers, although common, are nonspecific. Hyperferritinemia (>10,000 ng of ferritin per milliliter), however, appears to be characteristic of adult-onset Still's disease.[41]

Immune reconstitution syndrome, which represents aberrant reconstituted immunity to opportunistic pathogens on reversal of immunosuppression, is a new cause of FUO. However, this syndrome is not restricted solely to immunodeficient hosts. Long before human immunodeficiency virus (HIV) infection, illnesses consistent with but not recognized as immune reconstitution syndrome were observed with tuberculosis and leprosy as a result of the reversal of pathogen-related immunosuppression.[38] Fever in association with inflammatory tissue disease after microbiologic control of infection should arouse suspicion of immune reconstitution syndrome. Persons with HIV infection, organ-transplant recipients, postpartum women, neutropenic hosts, and recipients of anti–tumor necrosis factor α (TNF-α) therapy are at risk. Cryptococcosis, histoplasmosis, and mycobacterial infections are the most common opportunistic infections associated with immune reconstitution syndrome.[38]

Miscellaneous Causes and Drug-Associated Fever
Many other entities may cause classic FUO, some of which are listed in Table 4. An estimated 3 to 7% of febrile episodes in hospitalized patients are attributable to drugs.[45] However, drug-associated fever is frequently overlooked because of the lack of localizing signs. Eosinophilia, relative bradycardia, and rash are present in approximately 25%, 10%, and 5% of cases, respectively.[45] Nearly one third of drug-associated fevers are due to antibiotics, most commonly beta-lactams.[45] Drug reaction with eosinophilia and systemic symptoms (DRESS) is a distinct entity characterized by severe rash, fever, visceral involvement, lymphadenopathy, eosinophilia, and atypical lymphocytosis.

Hyperthermic drug syndromes, such as serotonin syndrome and neuroleptic malignant syndrome (Table 4), may be either idiopathic or known side effects of drugs.[42] Serotonin syndrome is caused by drugs that stimulate the 5-hydroxytryptamine family of serotonin receptors.[42,43] The incidence of this disorder is rising as a result of the increasing use of serotonergic drugs. Several nonprescription medications, illicit substances, and herbal products may also trigger serotonin syndrome when added to therapeutic serotonergic agents. Neuroleptic malignant syndrome is associated with dopamine receptor–blocking agents (e.g., antipsychotic agents) and may be misdiagnosed as serotonin syndrome. Laboratory abnormalities (e.g., leukocytosis) are characteristic of neuroleptic malignant syndrome, further confounding the diagnosis. Other causes of drug-associated fever are listed in Table 4.

NOSOCOMIAL FUO

Medical advances have led to an increased incidence of prolonged and unexplained fevers in hospitalized patients, a syndrome that often frustrates clinicians and that has been referred to as "fever of too many origins."[46] The workup for patients with nosocomial FUO overlaps with but is distinct from the workup for classic FUO, in that an evaluation for esoteric infections, autoimmune conditions, and cancers is typically not undertaken. The assessment, particularly in chronically critically ill patients, should initially focus on nosocomial infections, including vascular catheter–associated infections, urinary tract infections, pneumonias, intraabdominal infections, sinusitis, and *Clostridioides difficile* infection. Often, however, initial cultures and imaging studies are unremarkable.[46,47] Indeed, one study showed that 31% of febrile critically ill patients had noninfectious fevers, including neurogenic fevers due to cerebral injury, thromboembolic events, or drugs.[47] The frequency and degree of leukocytosis were similar for patients with infectious fevers and those with noninfectious fevers and thus could not be used reliably to distinguish between the two conditions.

Unexplained fevers are also commonplace in postsurgical patients. Most early-onset postoperative fevers are self-limited and are due to the

Table 2. Selected Zoonotic and Vectorborne Infections That May Cause FUO.*

Entity, Pathogens, and Syndromes	Region and Population (Seasonality)	Vector	Reservoir	Manifestations	Treatment	Comments
Rickettsioses						
Rickettsia rickettsii (Rocky Mountain spotted fever), *R. africae* (African tick bite fever), *R. typhi* (murine endemic typhus), *R. prowazekii* (epidemic typhus), *Orientia tsutsugamushi* (scrub typhus)	All continents except Antarctica (varies)	Ticks, fleas, lice, mites	Small mammals, including rats and flying squirrels (*R. prowazekii*)	Febrile syndromes with rashes (mild to fatal with DIC and encephalitis); inoculation ulcer uncommon	Tetracyclines	Tropism for vascular endothelial cells results in increased vascular permeability; thus, rash is expected in nearly all cases
Babesiosis						
Babesia species (e.g., *B. microti* in the U.S., *B. divergens* in Europe, *B. venatorum* in China)	Northeastern, southeastern, and upper midwestern U.S.; Europe; northeastern China (usually May–September)	*Ixodes scapularis* (deer tick); transfusion-related uncommon	White-footed mouse	Constitutional symptoms, hemolysis, ARDS; rash uncommon	Azithromycin plus atovaquone, clindamycin plus quinine	Rash should arouse suspicion of Lyme disease; immunocompromised and asplenic patients at risk for severe disease; coinfection with babesia, anaplasma, borrelia, and Powassan virus in the U.S.
Anaplasmosis						
Anaplasma phagocytophilum (human granulocytic anaplasmosis)	Northeastern and upper midwestern U.S.; central Europe; Asia (mainly spring and summer)	*I. scapularis*	White-footed mouse	Constitutional symptoms, fever, cytopenias, elevated aminotransferase levels; rash uncommon	Tetracyclines	Rash should arouse suspicion of Lyme disease; coinfection with babesia, anaplasma, borrelia, and Powassan virus in U.S.
Lyme disease						
Borrelia burgdorferi and other borrelia species, *B. mayonii* in upper midwestern U.S.	Northeastern and upper midwestern U.S.; Europe; Asia (June–August)	*I. scapularis* in the U.S.	Rodents (e.g., white-footed mouse)	Erythema migrans rash; cardiac, articular, neurologic manifestations; fever uncommon	Tetracyclines, amoxicillin, cefuroxime, ceftriaxone	Coinfection with babesia, anaplasma, borrelia, and Powassan virus in the U.S.; Jarisch–Herxheimer reaction with treatment can present as fever
Ehrlichiosis						
Ehrlichia chaffeensis (human monocytic ehrlichiosis), *E. ewingii*, *E. muris eauclairensis* (uncommon)	Southeastern, south-central, and mid-Atlantic U.S.; *E. muris* and *E. muris eauclairensis*: Minnesota and Wisconsin (spring and summer)	Lone Star tick (*Amblyomma americanum*); *E. muris* and *E. muris eauclairensis*: *I. scapularis*	White-tailed deer; *E. muris* and *E. muris eauclairensis*: white-footed mouse	Acute febrile illness, systemic symptoms, cytopenia, elevated aminotransferase levels; rash in up to 30% of patients	Tetracyclines	Unexplained fever may last between 17 and 51 days[31]

Disease	Cause	Geographic distribution	Transmission	Clinical features	Treatment	Comments
Bartonellosis	*Bartonella bacilliformis* (Oroya fever); *B. quintana*, *B. henselae* (bacteremia, culture-negative endocarditis, bacillary angiomatosis); *B. henselae* (cat scratch disease)	Oroya fever: valleys of Andes mountains; others: worldwide, homeless populations, persons with HIV infection (year-round)	Varies by organism and syndrome; sandflies, body lice, cat fleas	*B. bacilliformis*: humans; *B. quintana*: nonhuman primates; *B. henselae*: cats	Vary; fevers, constitutional symptoms, culture-negative endocarditis; lymphadenopathy with cat scratch disease; peliosis hepatis with bacillary angiomatosis	Varies by syndrome; tetracycline-based regimens often used; quinolones, rifampin, macrolides used	Survivors of Oroya fever are temporarily at risk for salmonellosis; cat scratch disease can be disseminated in immunocompromised hosts
Leptospirosis	*Leptospira interrogans* and other species	Ubiquitous and worldwide (variable; reportedly summer and fall)	Infection typically occurs after exposure to environmental sources (e.g., water/soil contaminated with animal urine)	Multiple mammals (e.g., rodents, cattle, horses)	Protean: fevers, constitutional symptoms, classic conjunctival suffusion; cough, myalgias, aseptic meningitis, pulmonary hemorrhage, jaundice; renal failure (Weil's disease)	Penicillin, tetracyclines	Inoculation into minor breaks in the skin or exposure of mucosal surfaces, occupational exposures (farmers, abattoir workers), adventure tourism
Brucellosis	Brucella species (e.g., *B. melitensis*, *B. abortus*, *B. suis*, *B. canis*)	Mediterranean basin, Middle East, Asia, Africa, Mexico, Central and South America (year-round)	Infection occurs after consumption or inhalation of or contact with infected animal products	Various mammals: sheep, goats, cattle, camels, dogs	Malaise, night sweats, arthralgias, back pain, constitutional symptoms; can lead to endocarditis, spondylitis, orchitis or epididymitis	Doxycycline, rifampin, TMP-SMX, ceftriaxone, aminoglycosides	Rare in the U.S. (consumption of imported, unpasteurized dairy products); special handling in microbiology laboratories; postexposure prophylaxis recommended for laboratory exposure
Q fever	*Coxiella burnetii*	Worldwide (year-round)	Ticks; animal feces, urine, placentas, or inhalation	Mammals (cattle, other farm animals), birds, arthropods	Fever, influenza-like illness, pneumonia, hepatitis; endocarditis, obstetrical complications	Varies; doxycycline, TMP-SMX, macrolides, hydroxychloroquine	Highest risk in persons in contact with farm animals, laboratory workers, and abattoir workers
Viral zoonoses	Hantavirus; Powassan, West Nile, Zika, dengue, and chikungunya viruses; St. Louis encephalitis; equine encephalitis virus; others	Vary; Powassan virus in northeastern U.S. and Great Lakes region; Russia (variable seasons)	Sandflies, mosquitoes, ticks (ixodes for Powassan virus)	Primates, birds, rabbits, rodents, cattle, others	Systemic febrile illness; rash, arthralgia, meningoencephalitis, cytopenia, hemorrhage, respiratory failure	Supportive	Illness ranges from self-limited (Zika virus) to potentially chronically debilitating (chikungunya and West Nile viruses) to fatal (hantavirus); consider coinfection with babesia, anaplasma, borrelia, and Powassan virus in U.S.

* Diagnosis of many of these entities can be challenging, and diagnostic testing (including serologic testing, polymerase-chain-reaction assay, and culture) may be insensitive or not readily available (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, for other entities that may cause FUO). ARDS denotes acute respiratory distress syndrome, DIC disseminated intravascular coagulation, and TMP-SMX trimethoprim–sulfamethoxazole.

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release of inflammatory cytokines in response to the physiological stress of surgery. Anastomotic leaks, fistulas, hematomas, acute gout flares (precipitated by volume depletion and tissue hypoxia), thromboembolic events, mesh- or graft-related infections, and *Mycoplasma hominis* infections after cardiac, orthopedic, or neurosurgical procedures are among the many causes of FUO after surgery. Contrary to popular belief, little evidence implicates atelectasis as a cause of fever.[48]

IMMUNODEFICIENCY AND FUO

The past several decades have seen the development of immunosuppressive and immunostimulatory therapies (e.g., biologic agents, monoclonal antibodies, checkpoint inhibitors, and chimeric antigen receptor [CAR]–modified T cells). Millions of adults in the United States currently receive immunosuppressive drugs.[49] Given the biologic variation among immunocompromising conditions, a uniform definition of immunodeficiency-associated FUO is not possible. Nonetheless, time- and quality-based criteria should generally be applied, though they may differ from the criteria used to define classic FUO as a result of underlying host factors.

Patients with HIV Infection
Fever in persons with HIV infection can be due to acute retroviral syndrome, which develops approximately 2 weeks after infection (coinciding with peak viremia) and is manifested as a mononucleosis-like syndrome and rash (Fig. 2E).[50] In persons with acquired immunodeficiency syndrome (AIDS), opportunistic infections and cancer represent the major causes of FUO. In a study from France in the early 1990s that evaluated 57 persons with AIDS and FUO, a cause was found in 86% of the patients. Mycobacterial infection, CMV infection, leishmaniasis, and lymphomas were the most common causes of fevers.[51] Other infections, including histoplasmosis, cryptococcosis, toxoplasmosis, and HHV-8 infection can occur in persons with AIDS.[52] However, antiretroviral therapy (ART) has transformed HIV infection into a chronic disease in which AIDS-related opportunistic infections rarely occur.[53] Thus, in the 21st century, HIV-associated FUO could be reclassified as FUO in persons receiving ART (for whom the workup should be similar to that for persons without HIV infection) and FUO in persons not receiving ART (Table 1). Immune reconstitution syndrome should be considered if FUO develops after the start of ART in a person with AIDS.

Organ-Transplant Recipients
FUO has been documented in 1.4% of 3626 organ-transplant recipients; more than half the episodes were due to infections.[54,55] With improved antiviral preventive treatment, CMV has become a less common cause of FUO. Other viral causes (e.g., EBV-related post-transplantation lymphoproliferative disease and infection with adenovirus, HHV-6, parvovirus B19, or HHV-8) remain a consideration in organ-transplant recipients with FUO.[54,55] The hyperinfection syndrome of *Strongyloides stercoralis* and disseminated histoplasmosis often elude diagnosis in febrile transplant recipients. Immunologic or surgical complications are additional sources of post-transplantation fever (Table 1). Serum sickness from antithymocyte globulin or alemtuzumab,[56] rejection that may be accompanied or preceded by eosinophilia, graft-versus-host disease (GVHD), and hemophagocytic lymphohistiocytosis, although rare, should also be considered in organ-transplant recipients with FUO.

Patients with Hematologic Cancers
Fever is universal in patients with hematologic cancers who are receiving remission-induction chemotherapy and before engraftment in recipients of hematopoietic-cell transplants. These persons are at high risk for prolonged and severe neutropenia, defined as an absolute neutrophil count of less than 500 per microliter for more than 7 days.[57,58] Fever during neutropenia is usually caused by translocation of endogenous bacterial or fungal flora into the bloodstream due to breaches in host defenses from neutropenia, mucositis, and catheters.[57,58] A causative agent is identified in only approximately a third of patients, and fever lasts for a median of 5 days despite appropriate antimicrobial therapy.[58] Patients with neutropenia in whom fever develops should be treated immediately with broad-spectrum antibiotics. If neutropenia and fever persist for more than 7 days, empirical antifungal therapy (primarily targeting molds) should be used. These cases are challenging to manage and should be assessed with daily examinations,

frequent cultures, imaging, and nonculture diagnostics to look for mold infections, with consideration of the status of the underlying cancer. In the absence of neutrophil recovery, FUO may be extremely protracted. Unless the patient's condition is deteriorating rapidly, "broadening" of antimicrobial agents should be avoided.

Fever may develop in hematopoietic-cell transplant recipients in the early postengraftment period as a result of engraftment, infectious or noninfectious pulmonary syndromes (e.g., the idiopathic pneumonia syndrome), fungal infection, reactivation of herpesviruses such as CMV, EBV, and HHV-6 (particularly with meningoencephalitis), adenovirus infection, hyperacute GVHD, or other factors. In the late postengraftment period, the causes of unexplained fever after hematopoietic-cell transplantation are extensive and include GVHD, opportunistic mold infections, post-transplantation lymphoproliferative disease, and cancer relapse (Table 1).

Fever occurs in approximately 92% of patients receiving CAR T-cell therapy.[57] Most febrile episodes develop within 3 weeks after such treatment and are considered to be due to the cytokine release syndrome (CRS). CRS-related temperatures can be very high, and although all patients receive antibiotics, the workup is often unrevealing. Given the lack of biomarker testing, CRS remains a diagnosis of exclusion when no other explanation for fevers can be ascertained early after CAR T-cell therapy. Because of the deleterious effect of high-grade CRS on clinical outcomes, the use of anticytokine therapies such as tocilizumab or glucocorticoids is recommended.[57]

Patients Receiving Other Immunosuppressive Therapies

A careful evaluation for common and opportunistic infections should be undertaken for all patients in whom fever develops during any iatrogenic immunosuppression. For instance, listeriosis, herpes zoster, and granulomatous infections (e.g., endemic mycoses, tuberculosis, or cryptococcosis) may develop in recipients of anti–TNF-α therapy.[59] Rituximab use has been linked with osteoarticular infections due to mycoplasma[60] and invasive ureaplasma infections.[61] In contrast, checkpoint inhibitor therapies that block T-cell inhibitory signals and increase immune responses to cancers may lead to a wide range of inflammatory reactions as a result of autoreactivity, including fevers without infections, organ inflammation, rash, and diarrhea.[62]

Table 3. Selected Malignant, Autoinflammatory and Autoimmune, and Miscellaneous Causes of FUO.*

Cancers

Lymphomas (including Hodgkin's and intravascular lymphomas); widespread metastatic carcinomas; tumors with liver metastases; colon, hepatocellular, and renal-cell carcinomas; acute leukemias; brain tumors with thermoregulatory disorders

Autoinflammatory and autoimmune disorders

Autoinflammatory: familial Mediterranean fever, Muckle–Wells syndrome, familial cold autoinflammatory syndrome

Autoimmune: autoimmune lymphoproliferative syndrome, autoimmune polyendocrinopathy syndrome

Variable autoinflammatory and autoimmune expression or mixed-pattern diseases†: giant-cell and Takayasu's arteritis, inflammatory bowel disease, certain types of uveitis, Behçet's syndrome, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis

Miscellaneous causes

Granulomatous, idiopathic, familial: idiopathic granulomatous hepatitis, granulomatosis with polyangiitis, chronic granulomatous disease, Rosai–Dorfman disease, adjuvant or silicone-induced granulomas, lipogranulomas (e.g., from mineral oil ingestion), Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis), Kawasaki's disease, sclerosing mesenteritis

Vascular: atrial myxoma, aortic dissection, deep-vein thrombosis, pulmonary emboli, hematoma, thrombophlebitis, intracranial hemorrhage and strokes

Endocrine: Addison's disease, thyrotoxicosis, thyroid storm, thyroiditis, pheochromocytoma

Hematologic: hemolytic–uremic syndrome, thrombotic thrombocytopenic purpura

Others: cirrhosis, pancreatitis, hemophagocytic lymphohistiocytosis, intravesical bacillus Calmette–Guérin, lipid overload syndrome (from lipid emulsion therapy), factitious fever, retroperitoneal fibrosis, crowned dens syndrome (calcium pyrophosphate deposition disease)

* Not all entities that may be associated with fever are shown; many other causes are described as case reports. Data are from Gaeta et al.,[17] Pannu et al.,[18] Loizidou et al.,[37] Sun and Singh,[38] and van Kempen et al.[39]
† These disorders may have both autoinflammatory and autoimmune components.

RETURNING TRAVELERS

The United Nations World Tourism Organization estimates that by 2030, approximately 2 billion people will travel annually, mostly to countries with emerging economies.[63] Although international tourism has declined because of the coronavirus disease 2019 (Covid-19) pandemic, febrile illnesses will continue to be encountered in tourists. Between 1996 and 2011, of 82,825 Western travelers who sought medical care, 4.4% had an acute illness; the most common

Table 4. Drug-Related Causes of Classic FUO.*

Type of Drug Reaction	Usual Time to Onset of Fever	Commonly Implicated Drugs or Other Agents
Hypersensitivity reaction	7–10 days	Antimicrobial agents (beta-lactams, sulfonamides, minocycline), allopurinol, anticonvulsants (phenytoin, carbamazepine), methyldopa, heparin, quinidine, quinine
Chemotherapy-related reaction	3–19 hr	Chemotherapeutic agents (cytosine arabinoside, bleomycin, chlorambucil, vincristine, cisplatin), molecular targeting agents for melanoma (dabrafenib, trametinib)
Infusion-related reaction	0.5–3.0 hr	Amphotericin B formulations, vancomycin, bleomycin, vaccines, monoclonal antibodies
DRESS	2–6 wk	Sulfonamides, carbamazepine, allopurinol, lamotrigine, phenytoin
Hyperthermia syndromes		
Serotonin syndrome	6 hr–several days†	Selective serotonin-reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline Serotonin–norepinephrine reuptake inhibitors: duloxetine, trazodone, desvenlafaxine, levomilnacipran, milnacipran, venlafaxine Tricyclic antidepressants: amitriptyline, nortriptyline MAO inhibitors: nonselective irreversible inhibitors (phenelzine, tranylcypromine), nonselective reversible inhibitors (linezolid), selective irreversible MAO type A inhibitor (methylene blue), selective irreversible MAO type B inhibitor (selegiline) Antiemetic agents: ondansetron, metoclopramide Serotonin receptor agonists: psychedelics (LSD), fentanyl, buspirone, triptans, lithium Herbal products: St. John's wort, Syrian rue (harmine and harmaline) Cytochrome P-450 inhibitors‡: fluoxetine, ciprofloxacin, ritonavir, fluconazole, sertraline
Malignant hyperthermia	0.5–2.0 hr	Depolarizing muscle relaxants: succinylcholine Inhalation anesthetics: halothane, sevoflurane, isoflurane, desflurane
Neuroleptic malignant syndrome	1–2 wk	Antipsychotic agents: haloperidol, quetiapine, olanzapine, risperidone Antiemetic agents: metoclopramide, prochlorperazine Parkinsonism–hyperpyrexia syndrome: abrupt withdrawal of dopamine agonists or non-dopaminergic agents (amantadine)
Adrenergic fever	Variable	Sympathomimetic agents and MAO inhibitors: theophylline, cocaine, MDMA (ecstasy)
Anticholinergic fever	About 2 hr	Anticonvulsants: carbamazepine Antiemetics: scopolamine, promethazine, prochlorperazine Muscle relaxants: cyclobenzaprine, methocarbamol, carisoprodol Herbal agents: belladonna, jimsonweed (datura), lupin Antidepressants: amitriptyline, imipramine, nortriptyline
Mitochondrial uncoupling of oxidative phosphorylation	0.5–3.0 hr	Pesticides and toxins: organochlorine compounds, snake venom–derived phospholipases Salicylates: high-dose aspirin

* Data are from McAllen and Schwartz,[42] Boyer and Shannon,[43] and Francescangeli et al.[44] DRESS denotes drug reaction with eosinophilia and systemic symptoms, LSD lysergic acid diethylamide, MAO monoamine oxidase, and MDMA 3,4-methylenedioxymethamphetamine.
† Agents with longer half-lives, such as fluoxetine, may precipitate the syndrome even if discontinued up to 5 weeks earlier.
‡ Cytochrome P-450–inhibiting isoenzymes (CYP2D6 and CYP3A4) may trigger serotonin syndrome when added to selective serotonin-reuptake inhibitors.

infections were malaria (in 76.9% of travelers), enteric fever (in 18.1%), and leptospirosis (in 2.4%).[64] The median time from travel to presentation was 16 days; 91% of the returning travelers had fever, and 0.4% died. Falciparum malaria was contracted mainly in West Africa, enteric fever in the Indian subcontinent, and leptospirosis in Southeast Asia.[64]

Recognition of life-threatening or transmissible travel-related infections should be a priority. These include viral hemorrhagic fevers (Table 2 and Table S1), leptospirosis, rickettsiosis (including typhus), measles, enteric fever, tuberculosis, influenza, severe coronavirus infections, and antibiotic-resistant bacterial infections.[65] Unless specifically considered, the diagnosis of many of these travel-related infections can be elusive. Many of these infections are preventable with vaccines. However, one study showed that only 19.7% of travelers with vaccine-preventable diseases had a health care encounter before traveling.[65]

DIAGNOSIS

Evaluation of FUO should begin with a thorough history taking, examination, and the initial diagnostic testing outlined in Figure 1. With this framework, clinicians should pursue potential diagnostic clues[6,23] to reach the final diagnosis. However, while diagnostic clues lead to a diagnosis in 62% of patients,[6] 48 to 81% of such clues may be misleading.[5,23] Since many FUO syndromes represent uncommon manifestations of common conditions, extensive, algorithm-driven laboratory evaluation should be discouraged, since it is expensive and may result in false positive results if the pretest probability of the condition is low. For instance, although measurement of procalcitonin levels is of potential value in persons with bacterial pneumonia, and beta-D-glucan assays may be of value in persons with invasive candidiasis or selected mold infections,[66] test results may be difficult to interpret in patients in stable condition who have undifferentiated febrile syndromes without a localizing source. Indeed, it would be imprudent to initiate antibacterial or antifungal therapy solely on the basis of elevated procalcitonin or beta-D-glucan values, without other reasons to suspect a bacterial infection or invasive mycosis (e.g., imaging findings, sepsis, or host factors). If the initial evaluation is unremarkable, additional elements of the history should be revisited, since diagnostic clues may emerge on repeat questioning. Temporal-artery biopsies have been proposed in elderly patients with unresolved FUO to look for temporal arteritis[67] and may be considered on a case-by-case basis. Laparotomies were commonly performed in persons with FUO decades ago[68] but have been replaced by computed tomographic (CT) imaging.

Two diagnostic methods that warrant mention are combined ^{18}F-fluorodeoxyglucose positron-emission tomography and CT (FDG PET-CT) (Fig. 2F) and next-generation sequencing. Meta-analyses have shown wide ranges in the performance of FDG PET-CT for FUO, with sensitivities ranging from 86 to 98% and specificities ranging from 52 to 85%.[69-72] The diagnostic yield of FDG PET-CT appears to be more than 50%,[69,72] and the yield is at least 30% greater than that of conventional CT.[69] The performance appears to be better in patients with infections or neoplasms than in those who have autoimmune conditions.[72] FDG PET-CT also appears to be superior to other nuclear imaging methods, such as PET without CT and gallium or leukocyte scintigraphy.[72] In addition, negative FDG PET-CT results appear to be associated with a high likelihood of spontaneous remission of fever.[70] Potential drawbacks of FDG PET-CT imaging include cost and limited availability in some centers.

Molecular diagnostic assays may overcome the limitations of traditional microbiologic testing, such as delayed results, reduced sensitivity with antibiotic use, and false negative serologic results early in the disease process.[73] These methods include next-generation sequencing, which involves unbiased sequencing of all genetic material in a specimen.[73] In addition, broad-range or pathogen-specific PCR assays targeting the 16S or 18S ribosomal RNA gene, D1–D2 region of ribosomal DNA, internal transcribed spacer, and other parts of bacterial and fungal genomes have gained widespread attention in recent years.[73] However, data on the routine use of molecular methods in cases of FUO are sparse,[73] and at present, these assays should be reserved for cases that remain undiagnosed (Fig. 1).

MANAGEMENT

It is often tempting to empirically administer antimicrobial or antiinflammatory therapy (e.g., glucocorticoids) in a patient with protracted fevers. However, unless the patient has neutropenia, is severely immunocompromised, or has a rapidly deteriorating clinical status, every attempt should be made to establish the diagnosis first. This is especially true for patients in whom FUO remains undiagnosed, since such patients have an excellent prognosis and may even have spontaneous remission.[74] Therapeutic antimicrobial trials may confer a predisposition to resistance or suppress the growth of fastidious pathogens and, in the case of self-limited conditions (e.g., viruses), may result in a false reassurance that the underlying cause of fever has been treated. Even antiinflammatory agents may lead to a delay in diagnosis if they result in resolution of fevers. In cases when the initial evaluation reveals diagnostic clues that strongly support a certain diagnosis (Fig. 1), clinical judgment should be used in deciding whether to pursue therapeutic chal-

lenges of drugs such as doxycycline, antituberculous medications, antifungal agents, glucocorticoids, and other therapies, pending the results of the diagnostic tests.

FUTURE DIRECTIONS

With the 20th century more than two decades behind us, it is time to eliminate dogmatic definitions of FUO from contemporary medical education, instead reframing FUO as a phenomenon of unexplained fever despite a nonrevealing, high-quality diagnostic workup after a reasonable amount of time has elapsed to rule out self-limited fevers. Advances in molecular diagnostics, such as DNA or RNA sequencing, which can rapidly detect multiple pathogens, and host-response biomarker technologies that use genomics, transcriptomics, proteomics, and metabolomics approaches may one day alter the diagnostic landscape of FUO, eliminating the need for a sharp clinical acumen to diagnose challenging cases.[75] These methods are unfortunately expected to be available only in high-income settings. Developing countries need access to rapid and reliable point-of-care testing that has implications for improving primary care management of febrile illnesses. Nonetheless, as the ability to diagnose FUO shifts from astute clinical judgment to molecular diagnostics, the field of FUO may one day enter the realm of precision medicine or perhaps even become completely obsolete.

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