Pediatric Fever of Unknown Origin

James W. Antoon, MD, PhD,* Nicholas M. Potisek, MD,† Jacob A. Lohr, MD††

*Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, University of Illinois at Chicago, Chicago, IL.
†Department of Pediatrics, Division of Pediatric Hospital Medicine, Wake Forest School of Medicine, Winston-Salem, NC.
††Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, University of North Carolina School of Medicine, Chapel Hill, NC.

Educational Gap

Pediatricians often confuse fever without a source and fever of unknown origin.

Objective

After completing this article, readers should be able to:

1. Adopt a systematic approach to evaluation and management of fever of unknown origin in patients of various ages.

CLINICAL PROBLEM

Fever is a common complaint in children. In most cases, fevers are due to self-limited viral infections and require no more than symptomatic treatment. Sometimes fever is due to common bacterial infections that are diagnosed by history and physical examination and require antibiotic treatment without laboratory evaluation. In a few clinical situations, the cause of fever is not easily identified. Fever without a source (FWS) may need further evaluation that includes laboratory tests or imaging. Rarely, the fever is more prolonged, requires more intensive evaluation, and falls in the category of fever of unknown origin (FUO).

There is often confusion about the terms FUO and FWS. Distinguishing between FUO and FWS is important and is based on duration of fever. FWS can progress to FUO if no cause is elicited after 1 week of fever.

The current incidence and prevalence of pediatric FUO remain unclear. Several factors contribute to the difficulty in determining the epidemiology, including the lack of a standardized definition, clinical criteria, and coding using the International Classification of Diseases-9 code for the condition. Furthermore, the causes of FUO often have an overlapping collection of symptoms and insidious disease courses. The general direction of the evaluation varies based on patient presentation, geographic location, associated symptoms, environmental exposures, physician experience, and available testing techniques.

FEVER PHYSIOLOGY

Body temperature is primarily controlled by the hypothalamus via regulation of pulmonary, skin, and metabolic systems. A basic understanding of the physiologic factors regulating temperature can help distinguish between normal variance and fever. The mean basal temperature varies according to age, gender, body habitus,

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time of day, activity level, menstrual cycle, and other factors. (1)(2) Importantly, physiologic temperature exhibits a morning nadir and an early evening peak, which can vary by as much as 1ºC. Furthermore, infants and young children maintain higher temperatures than older children and adults, primarily because of increased metabolic rate and body surface-to-weight ratio. (1)(3) Of note, core body temperature is positively related to obesity, which should be taken into account with the growing number of obese children in the United States.

Fever generally is defined as a core temperature of at least 38.0ºC (100.4ºF) and is the result of a complex series of signalling cascades initiated in response to specific biologic stimuli. (2) Fever is believed to provide an evolutionary advantage in fighting off infection. Bacteria and viruses are heat sensitive and exhibit temperature-dependent toxin production, growth, and response to antibiotics. (4)(5) The body's mechanism of increasing core temperature in response to infection functions to ward off the offending microbes. Increased metabolic rate accelerates immune system mobilization, lymphocyte transformation, lysosome and neutrophil activity, and phagocytosis. Increases in lipolysis and proteolysis diminish the amount of free glucose that can be used by invading organisms. Similarly, the body transiently removes iron, zinc, and copper, critical cofactors in viral and bacterial replication, from the blood in response to the presence of fever. (6) Taken together, the fever response provides a natural defense mechanism against invading pathogens.

DEFINITION OF FEVER OF UNKNOWN ORIGIN

One of the challenges in investigating and reviewing FUO is the lack of a standard definition. The number of fever days before considering FUO historically ranged from 5 to 21 and required some degree of medical evaluation. (7)(8) The original literature included a lengthy time course of up to 3 weeks, but the advent of improved and rapid laboratory techniques has led to a shortened number of fever days before considering FUO diagnoses. With the availability of rapid molecular diagnostic techniques for many infections, most of the common causes of FUO from the past can now be diagnosed or excluded rapidly, which has shortened the time that is required to move from FWS to FUO.

FUO has more recently been defined as a temperature higher than 38.0°C (100.4°F) that lasts longer than at least 8 days without a clear source. (9) Although most children meeting the definition of FUO would have had some laboratory assessment, it is not currently a prerequisite. (10) However, any previous evaluation would help to broaden or narrow the differential diagnosis.

CAUSES

FUO remains a diagnostic dilemma for many pediatricians because it is frequently difficult to distinguish clinically between benign and potentially life-threatening causes. The spectrum of FUO causes is broad and includes infectious, autoimmune, oncologic, neurologic, genetic, factitious, and iatrogenic (Fig 1). Pediatricians face the significant challenge of not missing the diagnosis of a serious illness or an easily treatable condition that can result in increased morbidity. Fortunately, FUO is usually an uncommon presentation of common diseases, most of which are easily treatable without increased morbidity.

Relatively few studies document the cause of FUO in developed countries; most of the current knowledge is derived from three studies performed almost 4 decades ago. (11)(12)(13) Low patient numbers and narrow patient populations in more recent studies limit the value of conclusions. (14)(15)(16)(17) More recent studies conducted in adult patients indicate a clear shift to noninfectious causes of FUO, but few corresponding studies confirm this shift in children. (10)(18)(19) Although numerous follow-up studies in developing countries catalogue the underlying causes of FUO, varying medical resources and endemic pathogens in these countries make it unclear whether such findings apply to the United States. (20)(21)(22)(23)(24)

The sentinel studies on pediatric FUO in the United States found that approximately 90% of cases had an identifiable cause: approximately 50% infectious, 10% to 20% collagen-vascular, and 10% oncologic. (11)(12)(13) Smaller subsequent studies from the 1990s had highly variable results: 20% to 44% infectious, 0% to 7% collagen-vascular, 2% to 3% oncologic, and up to 67% undiagnosed. (14)(15) The reason for this seemingly paradoxic increase in undiagnosed cases of FUO in the setting of improved diagnostic techniques is unclear. However, the shift from infectious to unidentifiable causes of FUO correlates with advances in diagnostic testing, including wider availability and rapid turnaround time. The advent of polymerase chain reaction, improved culture techniques, and better understanding of atypical viral and bacterial pathogenesis and autoimmune processes likely contribute to earlier diagnosis of the cause of FWS and fewer children advancing to the category of FUO. This shift to unidentifiable causes due to laboratory advances is supported by recent studies from developing countries with significant laboratory limitations, which show primarily infectious causes of FUO, similar to those of older studies in developed countries. (20)(21)(22)(23)(24)

Most cases of "undiagnosed" FUO appear to be benign, with many resolving spontaneously without a confirmed

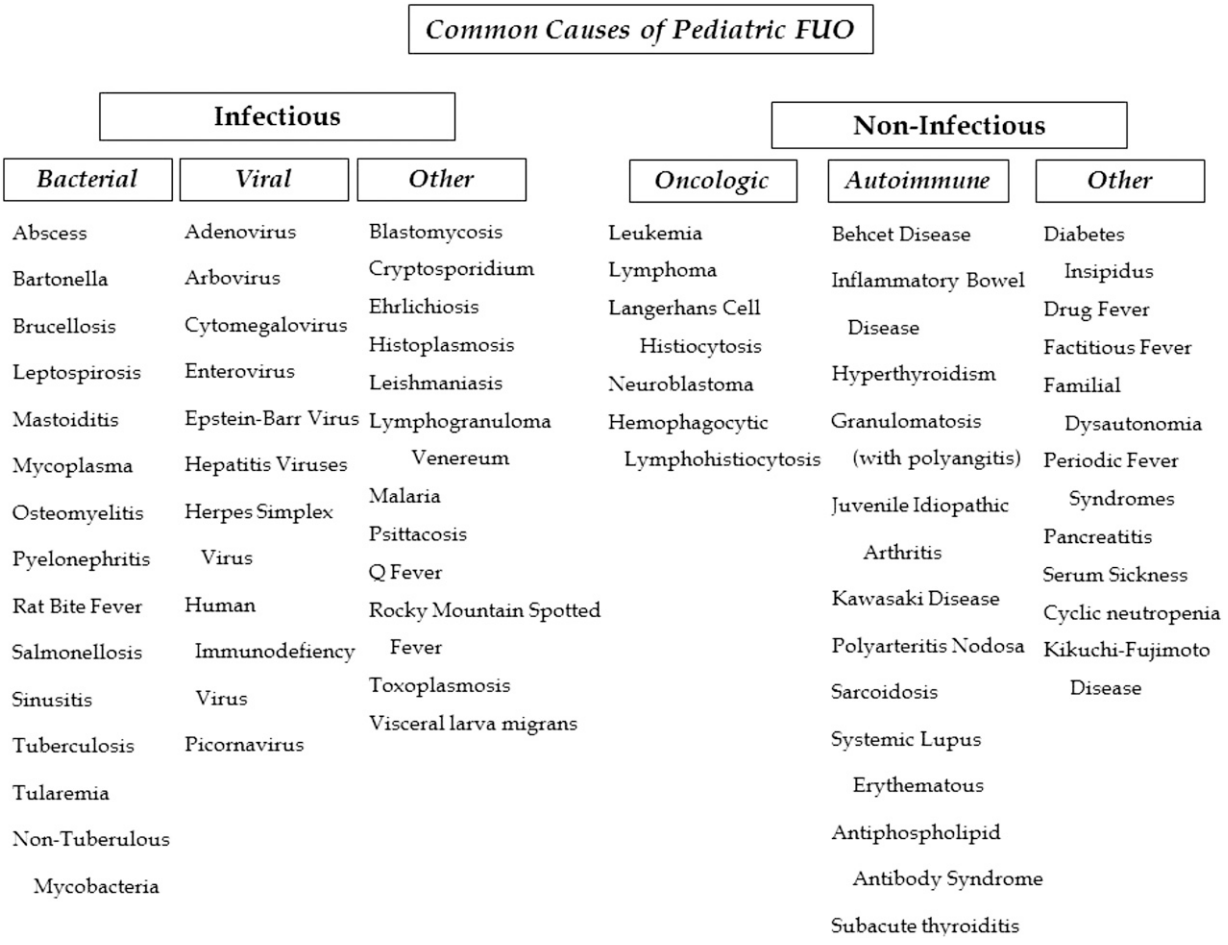

Figure 1. Causes of pediatric fever of unknown origin.

cause. These cases possibly consist of prolonged viral syndromes or difficult-to-confirm atypical bacterial infections. Substantially more evidence in the adult population supports the dynamic etiology of FUO over time, with multiple studies over several decades demonstrating an increasing trend toward undiagnosed cases. Some studies suggest that as many as 50% of adult FUO cases remain undiagnosed. (18)(19) These investigations also show decreased infectious and increased inflammatory diagnoses in the adult population over the same period of time. A better understanding of the current etiologic categories of FUO in children should improve the ability of medical practitioners to generate a differential diagnosis.

FEVER OF UNKNOWN ORIGIN IN DEVELOPING COUNTRIES

Recent literature from developing countries indicates that the causes of FUO remain primarily infectious. (20)(21)(22)(23)(24)(25) Chow et al (20) reviewed FUO causes in several developing countries from 1990 to 2008. In published studies with greater than 49 patients, infection (36%–78%) was by far the most common cause compared to other causes such as malignancy (2%–12%), collagen-vascular (2%–21%), miscellaneous noninfectious (2%–50%), and unknown (12%–29%). Most of these infections were of bacterial or atypical bacterial origin in contrast to the more common viral causes in developed countries. A more recent report of FUO in Turkey revealed a similar composition, with infection being most common, followed by malignancy and collagen-vascular diseases. (23) A 2012 study of 95 pediatric patients in Iran demonstrated that collagen-vascular diseases were more common causes than malignancy, but there was a high rate of undiagnosed cases. (26)

Interestingly, Chantada et al (25) reviewed 113 cases of FUO in Argentina according to three age categories: 0 to 11 months, 12 to 59 months, and older than 60 months. Infection was the most common cause across all age groups, but infectious causes were less common in those ages 12 to 59 months compared to the other two age groups. Children

ages 12 to 59 months had a corresponding increase in neoplastic and miscellaneous noninfectious causes of FUO. These results differed from a study of 80 patients in Turkey, which suggested a decreased likelihood of infectious causes with increasing age. (21) As with recent studies in developed countries, small sample sizes and variation in endemic infections limit generalization of these findings.

Several contributing and complicating factors are associated with the higher infectious burden of FUO in developing countries. The prevalence of certain infections known to cause FUO, such as human immunodeficiency virus (HIV), tuberculosis, leishmaniasis, and malaria, is higher in developing countries. Similarly, the rate of vaccine-preventable diseases is higher in developing compared to developed countries. Limited public health prevention programs and diminished access to health-care workers likely contribute to an increased incidence of infectious diseases as the cause for FUO, as does a decreased frequency of early recognition of infectious causes. Furthermore, limited awareness and ability to test for newly recognized causes of FUO, such as hemophagocytosis syndrome, may limit diagnosis of certain noninfectious causes.

EVALUATION

Initially distinguishing among infectious, autoimmune, malignancy, and miscellaneous causes of FUO may be difficult, but a thorough history and physical examination can often generate a directed differential diagnosis. We highly recommend a tiered approach to FUO to decrease overall costs and the use of invasive testing.

History and Physical Examination

Evaluation of FUO should be systematic and logically guided by history and physical examination findings. A detailed history, a thorough physical examination, and a proper interpretation of laboratory tests already performed are critical. The speed with which the evaluation should proceed and whether it should be outpatient or inpatient depends, in large part, on how ill the patient appears.

The first step in evaluating FUO is documentation that fever is actually present. Parental perception of fever often varies from the medical definition. It is useful to determine what the parent defines as fever and whether this varies from the medical definition of 38.0°C (100.4°F). In our experience, parents frequently report tactile or subjective fevers without actually measuring the patient's temperature with an instrument. Parents should be asked if the temperature was checked using a thermometer.

Pseudo-FUO has been defined as successive episodes of benign, self-limited infections with fever that the parents perceive as one prolonged fever episode. (27) This needs to be carefully ruled out before undertaking an expensive and unnecessary evaluation. Usually, pseudo-FUO starts with a well-defined infection (most often viral) that resolves but is followed by other febrile viral illnesses that may be less well defined. Diagnosis of pseudo-FUO usually requires a careful history, focusing on identifying afebrile periods between febrile episodes. Differentiating pseudo-FUO from real FUO can be challenging. If pseudo-FUO is suspected and the patient does not appear ill, keeping a fever diary can be helpful. In rare situations, a basic laboratory evaluation may be necessary.

Any associated symptoms and the timing of antipyretic administration is particularly important. A detailed description of the patient's fever pattern as intermittent (eg, tuberculosis), recurrent (periodic fever disorders), relapsing (rat bite fever), remittent (endocarditis, juvenile idiopathic arthritis [JIA]), or sustained (pyogenic abscess) can sometimes narrow the differential diagnosis. (12)(13) Information on the frequency and timing of fevers can be helpful in determining the fever curve and ability to document the fever in the medical setting. Periodicity of fever and the presence of other symptoms at the time fever is present can aid in making certain diagnoses, such as periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) or other periodic fever disorders, without further expensive evaluation. (28)

Fever can be the initial presentation of certain immunodeficiency syndromes, but many affected patients have a history of repeated infections, diarrhea, or abnormal physical findings, such as a rash. A history of atopy or autoimmune disease increases the likelihood of an autoimmune or rheumatologic cause. Furthermore, neutropenic fever in certain situations can be a medical emergency, and the presence of neutropenia may broaden the potential infectious sources of fever while narrowing the diagnostic possibility (eg, cyclic neutropenia). Determining the patient's risk factors for neutropenic fever and any associated signs and symptoms is an important step in an evaluation of FUO.

Information regarding the ethnicity, race, family history, and genetic background of the patient can be helpful. Periodic fever disorders often run in families and are more common in certain ethnicities. For example, familial dysautonomia is most common in the Ashkenazi Jewish population whereas familial Mediterranean fever is seen in those of Arab, Jewish, Armenian, and Turkish descent. (29)(30)

Geographic location and corresponding endemic pathogens known to cause FUO should be taken into consideration.

For example, coccidioidomycosis is more common in the southwestern United States and 60% of the cases of Rocky Mountain spotted fever are reported from North Carolina, Oklahoma, Arkansas, Missouri, and Tennessee. Travel to or residence in these areas is an important clue for making these diagnoses. A thorough travel history is critical in the evaluation of FUO and should include exposure to animals, unusual foods, insect bites, and sick contacts. Even if there is no travel history, clinicians should determine the patient's overall exposure to any domestic or wild animals (eg, home, school, woods, playground, friend's or relative's house) rather than simply asking "Do you have any pets?" when evaluating for zoonoses (Table 1) (For a more extensive list of zoonoses, see the table of diseases transmitted by animals in the *Red Book*.) Similarly, a thorough history of any sick contacts or high-risk exposures (eg, recent travel to foreign countries, prisons, the homeless) can help narrow the differential diagnosis based on epidemiologic factors.

Many causes of FUO are accompanied by associated symptoms. A detailed review of systems and their timing in relation to fever can lead to a diagnosis. Because many patients with FUO will have received a variety of treatments, it is important to determine whether therapeutic interventions may have influenced the disease or fever course. This is particularly important because drug fever is one of the causes of FUO and simply discontinuing a chronically administered agent may lead to fever resolution.

The most important aspect of evaluation for FUO is repeated history taking and encouraging the patient and family to report any new, different, or unusual signs or symptoms regardless of how trivial they may seem. Most cases of FUO are diagnosed because important historical information guides the direction of further evaluation.

A thorough physical examination should be performed that documents vital signs and any reported weight loss. Physical signs commonly provide evidence of the underlying diagnosis (Table 2). Serial physical examinations should be performed, and observation in a controlled inpatient setting may be beneficial because up to 25% of significant physical findings may be absent at the time of presentation.

TABLE 1. **Zoonoses and Fever of Unknown Origin**

EXPOSURE	ZOONOSES
Birds	Psittacosis, cryptosporidiosis, histoplasmosis, West Nile virus
Cats	*Bartonella henselae*, tularemia, *Pasteurella multocida*, rabies, *Capnocytophaga, Salmonella, Campylobacter, Cryptosporidium, Giardia lamblia, Toxoplasma gondii, Toxocara cati, Echinococcus, Ancylostoma braziliense, Dipylidium caninum*, leptospirosis, *Sporothrix schenckii, Microsporum canis*
Cows, Sheep, Goats	*Escherichia coli, Campylobacter, Salmonella, Cryptosporidium, Coxiella*, tularemia, *Brucella*
Dogs	Rabies, *Brucella, Pasteurella multocida, Capnocytophaga, Salmonella, Campylobacter, Giardia lamblia, Toxocara canis, Ancylostoma caninum, Echinococcus, Dipylidium caninum*
Ferrets	*Salmonella, Campylobacter*, cryptosporidiosis, toxocariasis, tuberculosis, leptospirosis, listeriosis, influenza, *Giardia, Mycobacterium microti*, rabies
Water (Fish, Water Mammals, Oysters Clams)	*Mycobacterium marinum*, schistosomiasis, *Vibrio parahaemolyticus, V vulnificus, Brucella Legionella, Pseudomonas, Parachlamydia, Giardia, Mycobacterium leprae, M avium, M marinum, M ulcerans, M simiae, Burkholderiaceae, Coxiella burnetii, Francisella tularensis, Enterobacteriaceae, Vibrionaceae, Listeria monocytogenes, Helicobacter pylori, Cryptococcus neoformans*
Squirrels	*Toxoplasma gondii, Rickettsia prowazekii*
Horses	*Salmonella, Campylobacter, Cryptosporidium, Giardia lamblia, Clostridium difficile, Brucella, Rhodococcus equi, Coxiella burnetii*
Insect Bites (Mosquitoes, Ticks, Fleas)	Malaria, *Trypanosoma cruzi*, equine encephalitis, West Nile virus, Lyme disease, ehrlichiosis, babesiosis, *Yersinia pestis*, tularemia, *Dirofilaria immitis*, leishmania, coltiviruses (Colorado tick fever), Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, babesiosis, Toscana virus
Rabbits	*Salmonella*, tularemia, *Yersinia, Cryptosporidium, Trichophyton, Pasteurella multocida*, rabies, babesiosis
Reptiles	*Salmonella, Edwardsiella tarda, Plesiomonas*, pentastomiasis
Rodents	Tularemia, leptospirosis, rat bite fever (*Streptobacillus moniliformis* and *Spirillum minus*), rabies, *Salmonella*, lymphocytic choriomeningitis virus, *Trichophyton*, hantavirus, *Pasteurella*

(11) On the other hand, completely normal physical examination findings at the time of the initial FUO evaluation are highly indicative of a benign underlying cause. (13)

During the evaluation, as the clinician expands the extent of laboratory and imaging assessment, repeated history taking and physical examinations are essential. They may reveal new information that could aid in determining appropriate laboratory and imaging studies.

Laboratory Studies and Imaging

A number of basic laboratory studies may be used to determine the source of FUO. A complete blood cell count (CBC) with differential count and smear can suggest an infectious or oncologic cause. Blood and urine cultures are recommended, with the understanding that repeat cultures may be needed. If the patient has neurologic symptoms, cerebrospinal fluid (CSF) studies are also indicated. Whenever possible, cultures should be obtained before initiating antibiotics to avoid ambiguity and contamination of results. Abnormalities in serum electrolytes or liver enzymes may indicate viral, atypical bacterial, or hematologic causes. Specific molecular testing for HIV, tuberculosis, or atypical bacterial pathogens and viral serologies is expensive and final results can be delayed days to weeks. These tests should be performed based on specific risk factors or suggestive physical findings.

Testing for acute-phase reactants, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin, is common in the evaluation of FUO. These tests results are nonspecific and not diagnostic of any particular disorder. On the other hand, elevated acute-phase reactants should encourage the physician to proceed with further appropriate evaluation. Of note, normal acute-phase reactant results do not exclude serious causes of FUO.

The CRP is a ring-shaped protein, consisting of five subunits, that is synthesized by the liver in response to inflammation. Detectable elevation of serum CRP occurs within 6 hours of the trigger, heightens to a peak, and resolves quickly following resolution of the stimulus. (32) Physiologic levels of CRP vary based on age, gender, obesity, exercise tolerance, sleep deprivation, and stress levels. Therefore, clinicians should note the relative elevation of CRP from baseline in the patient rather than rely on a single initial value. CRP can be pathologically elevated in a wide variety of disease processes, including inflammatory, infectious, and autoimmune. There has been much interest in CRP as a predictor of serious bacterial infection, and current evidence suggests that a markedly elevated CRP is required for specificity for bacterial infection. (33)(34)(35)(36) When evaluating FUO, particularly in the hospital setting, mildly elevated CRP values should not be used to rule in or out a particular disease process. Trending CRP values are a more valuable diagnostic tool and can be used to evaluate treatment response and direct treatment modalities. (37)

ESR responds to stimuli similar to those influencing CRP synthesis but is slower to elevate and has a longer half-life. ESR is an indirect measurement of serum acute-phase protein concentrations, and physiologic values vary based on age, gender, and other factors. Serum ESR may be altered in cases of abnormal serum protein concentrations, including fibrinogen, albumin, and immunoglobulin. In addition, ESR is subject to hemoglobin concentration and size, shape, and number of red blood cells. ESR is useful in determining chronic inflammation or infection, but for the previously stated reasons, it should be used with caution as a diagnostic tool, particularly in the setting of possible alterations in serum protein concentrations.

Ferritin is another acute-phase reactant. Elevated ferritin (in the absence of increased iron) may indicate an infectious, autoimmune, oncologic, or inflammatory process. (38) Some investigators have suggested that serum ferritin may be helpful in evaluation of FUO to distinguish between infectious and noninfectious causes. (39)(40) We have found that serum ferritin can be particularly helpful in diagnosing hemophagocytic lymphohistiocytosis (HLH), an increasingly recognized cause of pediatric FUO. (41) Recent guidelines have aided in the diagnosis of disease, and a serum ferritin value greater than 10,000 μg/mL is 90% sensitive and 96% specific for HLH. (42)(43)

Radiographs and imaging may play a role in the evaluation of FUO, but research suggests that empiric imaging has limited utility. (15) Chest radiographs should be performed if pulmonary symptoms are present or if there is concern for atypical bacterial infection, HIV, tuberculosis, or oncologic processes. Additional imaging techniques, particularly computed tomography (CT) scan and magnetic resonance imaging (MRI), are associated with various risks and should be performed discriminately. CT scans are known to increase the risk of leukemia and brain tumors, particularly in the pediatric population, and MRI is time-consuming and often requires sedation in young children. (44) Therefore, we recommend judicious imaging with specific diagnoses in mind. For example, in a patient with gastrointestinal symptoms, weight loss, and elevated CRP/ESR, an abdominal CT scan may aid in the diagnosis of inflammatory bowel disease, abscess, or cancer. Of note, all patients with a potential malignancy should receive a chest radiograph to evaluate for a mediastinal mass before CT scan or MRI to avoid airway complications while lying supine for imaging.

Other imaging modalities, such as white blood cell (gallium- or indium-111-labeled) scans, positron emission tomography, and immunoscintigraphy scanning, have not been well

TABLE 2. **Physical Findings and Associated Fever of Unknown Origin Diagnoses (31)**

SYSTEM	FINDING	ASSOCIATED ILLNESS
Abdomen		
	Hepatomegaly	Lymphoma, metastatic carcinoma, relapsing fever, granulomatous hepatitis, hemophagocytic lymphohistiocytosis, Q fever, typhoid fever, viral infections, salmonellosis, brucellosis, bartonellosis, endocarditis, malaria, leukemia
	Liver edge tenderness	Bartonellosis, liver abscess
	Splenic abscess	Infective endocarditis, brucellosis, enteric fever
	Splenomegaly	Leukemia, lymphoma, tuberculosis, brucellosis, infective endocarditis, cytomegalovirus, hemophagocytic lymphohistiocytosis, Epstein-Barr virus, psittacosis, relapsing fever, typhoid fever, Rocky Mountain spotted fever, Kikuchi-Fuijmoto disease
Chest		
	Murmur	Infective endocarditis, atrial myxoma
	Relative bradycardia	Typhoid fever, malaria, leptospirosis, psittacosis, central fever, drug fever
Eyes		
	Abnormal funduscopic examination findings	Miliary tuberculosis, toxoplasmosis, vasculitis
	Conjunctival suffusion	Leptospirosis, relapsing fever, Rocky Mountain spotted fever
	Conjunctivitis	Epstein-Barr virus, Newcastle disease, leptospirosis, Kawasaki disease (limbic sparing), tuberculosis, systemic lupus erythematosus, bartonellosis, chlamydial infection, histoplasmosis, tumor necrosis factor receptor-associated periodic syndrome, familial cold autoinflammatory syndrome
	Decreased pupillary constriction	Hypothalamic or autonomic dysfunction
	Dry eyes	Familial dysautonomia, systemic lupus erythematosus, polyarteritis nodosa, Sjögren syndrome
	Ischemic retinopathy	Polyarteritis nodosa
	Periorbital edema	Tumor necrosis factor receptor-associated periodic syndrome
	Subconjunctival hemorrhage	Endocarditis, trichinosis
	Uveal tract involvement	Tuberculosis, juvenile idiopathic arthritis, toxoplasmosis, sarcoidosis, systemic lupus erythematosus
Lymph Nodes		
	Lymphadenopathy	Lymphoma, bartonellosis, tuberculosis, lymphogranuloma venereum, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, toxoplasmosis, juvenile idiopathic arthritis, brucellosis, Kikuchi-Fuijmoto disease, tularemia, viral infections, mycobacterial infection, leukemia, hyperimmunoglobulin D syndrome, familial cold autoinflammatory syndrome
Genitourinary		
	Epididymo-orchitis	Tuberculosis, lymphoma, brucellosis, leptospirosis, Epstein-Barr virus, blastomycosis, carcinoma
Musculoskeletal		
	Bone tenderness	Osteomyelitis, malignancy, infantile cortical hyperostosis
	Costovertebral tenderness	Chronic pyelonephritis, perinephric abscess
	Hyperactive reflexes	Hyperthyroidism

Continued

TABLE 2. (Continued)

SYSTEM	FINDING	ASSOCIATED ILLNESS
	Hypoactive reflexes	Familial dysautonomia
	Joint tenderness	Familial Mediterranean fever, rat-bite fever, systemic lupus erythematosus, Lyme disease, lymphogranuloma venereum, brucellosis, hyperimmunoglobulinemia D syndrome, tumor necrosis factor receptor-associated periodic syndrome
	Muscle tenderness	Brucellosis, trichinellosis, arboviral infection, dermatomyositis, polyarteritis, subdiaphragmatic abscess (trapezius tenderness)
	Spinal tenderness	Subacute vertebral osteomyelitis, infective endocarditis, brucellosis, typhoid fever
Oropharynx		
	Anomalous dentition	Anhidrotic ectodermal dysplasia
	Dental or fascial abscess	Sinusitis, brain abscess, mediastinal abscess
	Epistaxis	Relapsing fever, leukemia, psittacosis, rheumatic fever
	Gingival hypertrophy	Leukemia, Langerhans cell histiocytosis
	Pharyngeal hyperemia	Cytomegalovirus, Epstein-Barr virus, toxoplasmosis, tularemia, leptospirosis
	Smooth tongue	Familial dysautonomia
	Ulcerations	Behçet disease; periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA); hyperimmunoglobulin D syndrome
Skin (limited review)		
	Blotchy skin	Familial dysautonomia
	Decreased body hair, hypohidrosis	Anhidrotic ectodermal dysplasia
	Dehydration	Diabetes insipidus, ectodermal dysplasia, familial dysautonomia
	Erythema nodosum	Infection, juvenile idiopathic arthritis, systemic lupus erythematosus, malignancy, inflammatory bowel disease
	Erythema migrans	Lyme disease, southern tick-associated rash illness (STARI)
	Eschar	Tularemia
	Macular salmon-pink rash	Juvenile idiopathic arthritis
	Malar erythema	Systemic lupus erythematosus
	Palpable purpuric lesions	Polyarteritis nodosa
	Petechiae	Endocarditis, bacteremia, viral infection, rickettsia
	Seborrheic rash	Histiocytosis
	Urticarial macular rash	Serum sickness, familial cold autoinflammatory syndrome, Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease

studied in the diagnosis of pediatric FUO. Limited evidence in children and additional studies in adults suggest that these techniques have low sensitivity and specificity in the evaluation of FUO and should be used only if traditional imaging fails to reveal a diagnosis. (45)(46)(47)(48)

If fever persists and laboratory studies and imaging fail to reveal the underlying cause, invasive procedures may be necessary. Bone marrow biopsy can be performed to evaluate for oncologic or hematologic etiologies. Lumbar puncture, thoracentesis, joint aspiration, or biopsies may also be indicated to obtain fluid or tissue for analysis. These should be performed as a last resort in the non-acute patient.

Initial Diagnostic Approach

We recommend that the initial laboratory evaluation of pediatric FUO consist of a CBC, basic metabolic panel,

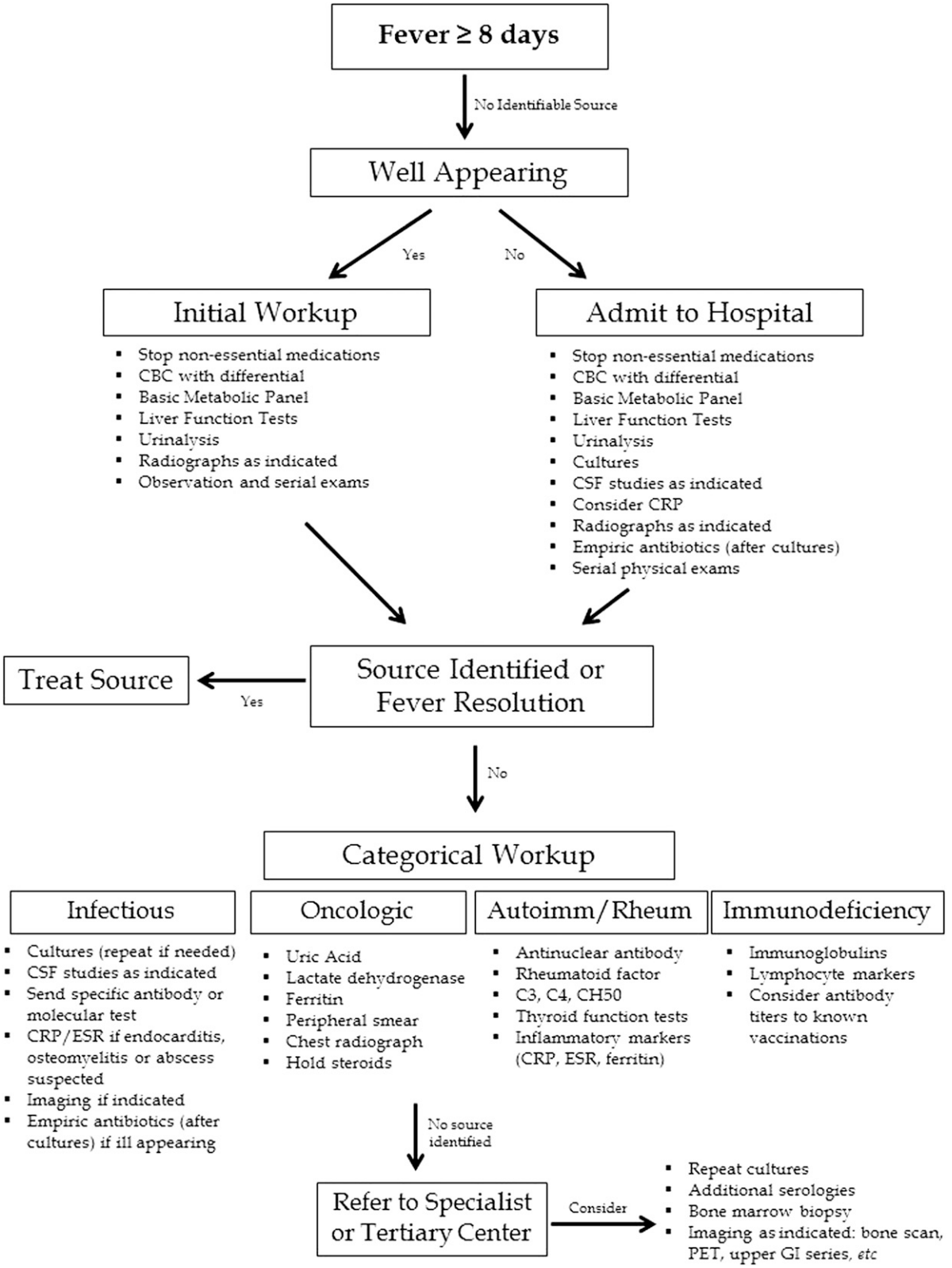

Figure 2. Focused approach to fever of unknown origin based on suspected disease category.

liver function tests, urinalyses, and blood and urine cultures. If the patient has neurologic symptoms, CSF studies may be considered. These tests should be performed before initiating treatment to prevent contamination of results.

The evaluation of FUO should be targeted if any findings on history, physical examination, or laboratory and imaging evaluation direct suspicion toward an organ system or diagnosis. A patient with known tick exposure, rash, and hyponatremia should receive serologic evaluation for Rocky Mountain spotted fever, Lyme disease, ehrlichiosis, anaplasmosis, or babesiosis, depending on the endemic region or travel history. (49) When deciding which laboratory tests to order, it is important to note that uncommon presentations of common diseases are more likely to cause FUO than uncommon or rare diseases. A well-appearing child with fever, rash, lymphadenopathy, and transaminitis is more likely to have Epstein-Barr virus or cytomegalovirus infection rather than HLH or systemic lupus erythematosus. In a nonacute patient, ruling out common causes of FUO before testing for uncommon causes or performing invasive testing can minimize the likelihood of dealing with false-positive, false-negative, or equivocal results for rare diseases.

We have established an initial diagnostic algorithm based on the broad etiologic categories of FUO that may be performed if a practitioner is suspicious for a particular disease process (Fig 2). The recommended evaluation provides diagnostic "first steps" in the evaluation of these categories that may be performed before referral for specialized or invasive testing. This tiered approach to FUO can decrease overall costs and the use of invasive testing.

MANAGEMENT AND EMPIRIC TREATMENT

The initial management of FUO remains an area of debate. Pediatric FUO is often overtreated because most cases are caused by benign or nonacute disease. Physician concern for serious illness or parental pressure can lead to empiric treatment before sufficient evaluation. Physicians may be inclined to start antipyretics, corticosteroids, or antibiotics for an unknown disease process, which can affect future laboratory data, imaging, or treatment. Many cases of FUO resolve without a diagnosis and empiric treatment may mask the diagnosis of life-threatening oncologic, infectious, and autoimmune diseases. Empiric treatment should be initiated with caution and in conjunction with judicious testing.

The first step in the management of FUO is to discontinue all nonessential pharmacologic agents, including antipyretic medications. Drug fever can manifest at any time after starting a medication, with an overall incidence of up to 5%. (50) Drug fever is a common source of FUO and can be caused by any agent, including antibiotics, ibuprofen, and acetaminophen (Table 3). Once the drug is discontinued, fever usually abates within 24 hours or two half-lives of the drug, typically resolving within 72 to 96 hours. (51) If drug fever is suspected and the patient is taking multiple medications, eliminating one drug at a time may be helpful in identifying the offending agent. However, other causes of fever should be explored, based on history and physical

TABLE 3. **Common Causes of Drug Fever**

CLASS	DRUGS
Antimicrobial agents	Acyclovir, carbapenems, cephalosporins, tetracyclines, mebendazole, nitrofurantoin, penicillins, rifampin, sulfonamides, vancomycin
Anticonvulsants	Barbiturates, carbamazepine, phenytoin
Antidepressants	Doxepin, nomifensine
Antineoplastic agents	6-mercaptupurine, bleomycin, chlorambucil, cisplatin, cytosine arabinoside, daunorubicin, hydroxyurea, interferon, L-asparaginase, procarbazine, streptozocin, vincristine
Cardiovascular drugs	Clofibrate, diltiazem, dobutamine, furosemide, heparin, hydralazine, hydrochlorothiazide, methyldopa, oxprenolol, procainamide, quinidine, triamterene
Histamine-2 blockers	Cimetidine, ranitidine
Immunosuppressants	Azathioprine, everolimus, mycophenolate mofetil, sirolimus
Nonsteroidal anti-inflammatory drugs	Ibuprofen, sulindac, phenothiazines, salicylates
Other	Allopurinol, antihistamines, folate, herbal remedies, iodide, metoclopramide, piperazine, propylthiouracil, prostaglandin E2, ritodrine, sulfasalazine, sympathomimetics, theophylline, thyroxine

examination findings, when discontinuing the medication to ensure that fever resolution is due to drug fever rather than resolution of another cause.

In an otherwise healthy, well-appearing child with FUO, we do not recommend routine use of empiric antibiotics or anti-inflammatory agents. Empiric antibiotics can delay the diagnosis of common infectious causes of FUO, such as endocarditis, osteomyelitis, central nervous system infection, or abscesses. Pediatricians commonly prescribe tetracyclines (namely, doxycycline) or macrolides for presumed atypical bacterial infections in the absence of risk factors or clinical criteria for these diseases. These agents have activity against some typical bacteria and have limited anti-inflammatory effects, which can delay the manifestation or natural disease process of alternative causes of FUO. (52)(53)(54) We recommend the use of these agents when there is high clinical suspicion and only after the diagnostic tests for the pathogen are obtained.

The decision to use empiric anti-inflammatory agents is challenging. Corticosteroids can play a significant role in treating certain causes of FUO, such as autoimmune disease. There is no urgency for empiric treatment in most autoimmune diseases, and treatment should be started after the diagnosis is confirmed. On one hand, corticosteroids affect a broad range of physiologic processes, including the immune system; can potentially increase the risk of acquiring an infection or worsen an underlying infection; and can impair the diagnostic usefulness of blood and tissue samples in oncologic testing and staging. On the other hand, immune suppression should not be a contraindication for specifically indicated short-term corticosteroids. Clinical immune suppression associated with corticosteroid use manifests after 14 to 21 days of daily administration. (55)(56)(57)(58) We recommend the use of corticosteroids if there is high suspicion for serious autoimmune and inflammatory conditions, such as systemic lupus erythematosus or JIA, but not until oncologic etiologies have been excluded.

PROGNOSIS AND OUTCOME

A major difference between adult and pediatric FUO is outcome. The prognosis of pediatric FUO is likely favorable compared to FUO in the adult population due to differences in causes. (59)(60) The original studies on pediatric FUO from the 1970s demonstrated a mortality rate of 6% to 9%. (12)(13) However, with the shifting causes of pediatric FUO, further study is needed to define outcomes in both adult and pediatric cases.

The increasing percentage of "undiagnosed" causes of FUO has influenced the previously documented pediatric mortality rates. Recent evidence suggests reassuring outcomes for undiagnosed pediatric FUO. Talano and Katz (17) followed 19 children with undiagnosed FUO for a median of 3.5 years. Sixteen of 19 (82%) children with initially undiagnosed FUO were afebrile and clinically healthy at long-term follow-up. Of the three children who remained febrile or were not clinically well, two were subsequently diagnosed with JIA and the other with intussusception. Similarly, Miller et al (16) studied 40 children referred to a rheumatology clinic for evaluation of FUO. Of the 40 children, 37 were available at long-term follow-up (median 60.5 months); 34 had complete resolution of fevers and 2 (5%) developed evidence of inflammatory bowel disease during follow-up. Of note, neither of these studies was powered for morbidity or mortality analysis. Whether the mortality rate of 6% to 9% found in previous studies applies to current cases of FUO is currently unknown, particularly given the evolving changes in underlying etiology over time. Further study is needed to determine the mortality and overall outcomes associated with pediatric FUO.

Summary

- On the basis of strong clinical evidence, the causes of FUO are broad and include both benign and life-threatening medical conditions. (12)
- On the basis of observational studies, most cases of FUO have shifted to noninfectious etiologies over the past several decades. (10)
- On the basis of observational studies, completely normal physical examination findings at the time of the initial FUO evaluation suggest a benign underlying cause. (13)
- On the basis of consensus and expert opinion, a stepwise, tiered approach to FUO should be implemented to decrease cost and time to diagnosis. (13)

References for this article are at http://pedsinreview.aappublications.org/content/36/7/380.full.

Parent Resources from the AAP at HealthyChildren.org

- https://www.healthychildren.org/English/health-issues/conditions/fever/Pages/When-to-Call-the-Pediatrician.aspx
- Spanish: https://www.healthychildren.org/spanish/health-issues/conditions/fever/Paginas/When-to-Call-the-Pediatrician.aspx

PIR Quiz

1. A 5-year-old female has had a fever to 39.7°C (103.6°F) once or twice daily for 8 days. Her pediatrician notes on history complaints of body aches and fatigue. Other than fever, there are no abnormal findings on physical exam. Which of the following is the most likely diagnosis at this time?
    A. Bacteremia.
    B. Fever of unknown origin (FUO).
    C. Fever without a source.
    D. Influenza.
    E. Rheumatoid arthritis.
2. Which of the following best describes usual etiologies of FUO?
    A. A common presentation of an uncommon disease.
    B. An uncommon presentation of a common disease.
    C. An untreatable disease with increased morbidity.
    D. A relatively serious disease that is usually treatable.
    E. A relatively uncommon disease requiring minor or no treatment.
3. Based on sentinel studies, which of the following are the most common identifiable etiologies of FUO in the United States?
    A. Allergic diseases.
    B. Autoimmune diseases.
    C. Collagen vascular diseases.
    D. Infectious diseases.
    E. Oncologic diseases.
4. A 10-year-old male presents with a 14-day history of FUO. His elevated temperature to 40.1°C (104.2°F) has been relatively sustained throughout this time period. Which of the following etiologies based on this fever pattern most likely underlies this child's problem?
    A. Endocarditis.
    B. Juvenile idiopathic arthritis.
    C. Pyogenic abscess.
    D. Rat bite fever.
    E. Tuberculosis.
5. Periodic fever disorders often run in families and are more common in certain ethnicities. Among which of the following ethnic groups is familial dysautonomia most common?
    A. Arab population.
    B. Armenian population.
    C. Ashkenazi Jewish population.
    D. Sephardic Jewish population.
    E. Turkish population.

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