RESEARCH ARTICLE

Etiology and Resource Use of Fever of Unknown Origin in Hospitalized Children

James W. Antoon, MD, PhD,[a] David C. Peritz, MD,[b] Michael R. Parsons, MD,[c] Asheley C. Skinner, PhD,[d] Jacob A. Lohr, MD[e]

ABSTRACT

BACKGROUND: Fever of unknown origin (FUO) is a well-known pediatric presentation. The primary studies determining the causes of prolonged fever in children were performed 4 decades ago, before major advances in laboratory and diagnostic testing. Given that the distribution of diagnosed causes of adult FUO has changed in recent decades, we hypothesized that the etiology of FUO in children has concordantly changed and also may be impacted by a definition that includes a shorter required duration of fever.

METHODS: A single-center, retrospective review of patients 6 months to 18 years of age admitted to the North Carolina Children's Hospital from January 1, 2002, to December 21, 2012, with an *International Classification of Diseases, Ninth Revision* diagnosis of fever, a documented fever duration >7 days before admission, and a previous physician evaluation of each patient's illness.

RESULTS: A total of 1164 patients were identified, and of these, 102 met our inclusion criteria for FUO. Etiologic categories included "infectious" (42 out of 102 patients), "autoimmune" (28 out of 102 patients), "oncologic" (18 out of 102 patients), and "other" or "unknown" (14 out of 102 patients). Several clinical factors were statistically and significantly different between etiologic categories, including fever length, laboratory values, imaging performed, length of stay, and hospital costs.

CONCLUSIONS: Unlike adult studies, the categorical distribution of diagnoses for pediatric FUO has marginally shifted compared to previously reported pediatric studies. Patients hospitalized with FUO undergo prolonged hospital stays and have high hospital costs. Additional study is needed to improve the recognition, treatment, and expense of diagnosis of prolonged fever in children.

[a]*Department of Pediatric and Adolescent Medicine, Children's Hospital, University of Illinois Hospital & Health Sciences System, Chicago, Illinois;* [b]*Division of Cardiovascular Medicine, University of Utah School of Medicine, Salt Lake City, Utah;* [c]*Department of Pediatrics, Johns Hopkins Children's Center, Baltimore, Maryland;* [d]*Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina; and* [e]*Department of Pediatrics, University of North Carolina at Chapel Hill School of Medicine and North Carolina Children's Hospital, Chapel Hill, North Carolina*

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Address correspondence to James W. Antoon, MD, PhD, Department of Pediatric and Adolescent Medicine, Children's Hospital, University of Illinois Hospital & Health Sciences System, 840 S Wood St, Chicago, IL 60612. E-mail: jantoon@uic.edu

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Fever of unknown origin (FUO) is a well-known pediatric presentation. FUO remains a dilemma for pediatricians because of the difficulty in differentiating between benign and life-threatening causes. The causes of FUO are broad, and common etiologies include infectious, collagen-inflammatory (autoimmune), oncologic, neurologic, genetic or congenital, pharmacologic, miscellaneous, and iatrogenic diseases.[1] Although the etiologies of FUO have been extensively studied in adults, there is limited literature on FUO in children.[1,2]

Authors of recent studies in adults demonstrate the dynamic nature of FUO over time. In the past 30 years, the most common identifiable FUO etiologies in adults changed from infectious to inflammatory diseases. Notably, however, the most common final diagnosis for FUO in adults is now "unknown" or "no diagnosis."[2–4] In pediatric studies, authors have demonstrated relative differences in FUO etiologies compared with adults and there are limited data to determine if etiologic categories of FUO have similarly changed in children.[5–7]

We performed a large retrospective FUO etiology study on children hospitalized in a single center in the United States, similar to the 3 seminal FUO studies performed in the 1970s. The primary objectives of this study were to (1) determine the current etiology of pediatric FUO and (2) characterize the demographic epidemiology of FUO in an inpatient pediatric population to determine if the causes of FUO have changed over time.

METHODS

Study Design

A comprehensive retrospective chart review was performed on hospitalized pediatric patients 6 months to 18 years of age admitted to the North Carolina Children's Hospital from January 1, 2002, to December 21, 2012. For study purposes, FUO was defined as fever of 38.0°C or greater for >7-days duration without an identifiable source on presentation to the hospital.[1] Inclusion criteria were defined as an *International Classification of Diseases, Ninth Revision* diagnosis of fever (780.60 or 780.61). A chart review was then performed to evaluate for additional inclusion criteria including fever defined as FUO above and an evaluation by a medical provider during the period of fever. Exclusion criteria included known or presumed source of fever at the time of presentation to the hospital. The study was approved by the University of North Carolina Institutional Review Board (IRB#13-1110).

Data Collection

Patients were identified by using the Carolina Data Warehouse, which collects information on all patients admitted to the University of North Carolina health care system. On identification of potential patients, a retrospective chart review was performed on each patient to determine eligibility and collect information on study variables. Available historical and physical examination data, demographics, laboratory studies, imaging studies, pathology studies, hospital costs (defined as hospital charges), and billing information were reviewed for each patient.

Patient Population

After chart review, patients were subdivided into cohorts on the basis of duration of fever and etiologic category. Duration of fever cohorts included the following 3 groups: 8 to 14 days, 15 to 21 days, and >21 days. The duration cohorts were chosen on the basis of previously published definitions of FUO in children, which have defined FUO as >7,[1] 14,[7,8] or 21[5,6,9] days of fever. Category cohorts in this study included the following: autoimmune, infectious, oncologic, and other or unknown. The cohort categories chosen were similar to those in previously published studies.[1,5–7,9] Cohorting patients by duration of fever and etiologic category allowed us to determine if duration of fever in the definition of FUO was associated with changes in underlying FUO categories.

Statistical Analysis

We used χ^2 tests (for categorical variables) and F tests (for continuous variables) to describe differences in demographics, diagnostic testing conducted, and laboratory values, by length of fever and etiology. Finally, we examined length of stay (LOS) and hospital cost by length of fever and etiology. All analyses were conducted by using Stata 14.0 (StataCorp, College Station, TX).

RESULTS

Study Demographics

We identified 1164 patients who met initial inclusion criteria during the study period. Of these, 102 (mean of 9.3 cases per year) patients met our inclusion definition for FUO and previous evaluation by a medical provider. Nineteen qualifying patients were missing information on race, 6 were missing information for age, 5 were missing information for sex, and 2 were missing admission temperatures in the administrative database. Mean age on admission was 6.5 years; 56.9% were boys (Table 1). There were no significant differences in age, sex, or race when compared by fever duration and FUO category.

Initial Presentation and Fever

Although all patients had a documented fever for >7 days before hospitalization, a majority of children (65.0%) did not have fever at any time during their emergency department visit. However, 82.2% of children

TABLE 1 Patient Demographics and Duration of Fever on Admission

Demographic	Total *n* (%)
N	102 (100)
Age, y	
0–5	57 (55.9)
6–10	14 (13.7)
>10	26 (25.5)
Unknown	5 (4.9)
Mean age, y	6.5
Sex	
Boys	58 (56.9)
Race and/or ethnicity	
White	41 (40.2)
African American	24 (23.5)
Hispanic	13 (12.8)
Other ethnicity	2 (2.0)
Unknown ethnicity	22 (21.6)
Fever on admission	37 (36.2)
Fever during hospital stay	84 (82.4)
Complex chronic condition	26 (25.5)
Final etiologic category	
Autoimmune	28 (27.5)
Infectious	42 (41.2)
Oncologic	18 (17.7)
Other or unknown	14 (13.7)

TABLE 2 Categorization of Pediatric FUO Etiologies

Infectious (n = 42)	Autoimmune (n = 28)	Oncologic (n = 18)	Other or Unknown (n = 4/10)
Acute bacterial sinusitis	Autoimmune disorder of unknown etiology	Acute lymphoid leukemia	Drug fever
Aseptic meningitis	Atypical Kawasaki	Hepatocellular carcinoma	Autonomic instability
Bartonella meningitis	Bechet's disease		Hemophagocytic lymphohistiocytosis
Bartonella osteomyelitis	Bechet's disease with Hughes-Stovin syndrome		Macrophage activating syndrome
Diskitis	Crohn's disease		Unknown
C difficile colitis	Dermatomyositis		
Candida albicans infection	Erythema multiforme		
Cytomegalovirus	Juvenile idiopathic arthritis		
Epstein-Barr virus infection	Kawasaki disease		
Empyema	Periodic fever syndrome (unspecified)		
Endocarditis	Vasculitis of unknown etiology		
Enterovirus infection	Systemic lupus erythematosus		
Ehrlichiosis meningitis			
Gluteal abscess			
Fungemia			
Herpes stomatitis			
Infected brachial cleft cyst			
Intraabdominal abscess			
Meningitis			
Metapneumovirus infection			
Parapneumonic effusions			
Pneumonia			
Pyelophlebitis			
Septic joint (knee)			
Staphylococcus infection			
Tracheitis			
Viral illness			

had at least 1 documented febrile episode during their hospital stay. Children without fever on admission were more likely to have a longer reported duration of fever ($P < .05$).

FUO Etiology and Categorization

The identified etiologies of FUO by category are listed in Table 2. Overall, the most common FUO category was infectious (41.2%, 42 out of 102 patients), followed by autoimmune (27.5%, 28 out of 102 patients), oncologic (17.7%, 18 out of 102 patients), and unknown or other (13.7%, 14 out of 102 patients). The most common underlying cause of FUO in all fever duration subgroups were infectious (Table 3). Autoimmune etiologies were more common with early FUO (36.6% of those with 8–14 days of fever) and had the lowest prevalence in those with 15 to 21 days of fever (15.8%). Children with an autoimmune etiology of FUO were younger than those with other etiologies ($P < .05$). Unlike the patients in other categories, the patients ultimately diagnosed with unknown or other diagnosis were more likely to fall into the group with >21 days of fever (Table 3).

Diagnostic Evaluation of FUO

Every patient received at least 1 culture and 1 imaging study within the first 24 hours of admission. Specimens for bacterial culture were frequently obtained, with blood (80.4%) and urine (46.1%) cultures being most commonly performed. Although every patient received at least 1 bacterial culture, not a single culture result was reported as positive. Viral studies were performed in 43.1% of patients and results were positive in 8.8% of patients. The most common imaging studies were radiographs, performed in 70.6% of patients, followed by ultrasounds (47.1%), MRI (9.8%),

TABLE 3 Etiologic Category and Duration of Fever ($P < .05$)

	Fever Duration			
	>8–14 d, %	>15–21 d, %	>21 d, %	Total, %
Infectious disease	40.0	63.2	34.2	42.2
Autoimmune	33.3	15.8	21.1	25.5
Oncologic	20.0	15.8	15.8	17.7
Other or unknown	6.7	5.3	29.0	14.7

computerized tomographies (7.8%), and bone scans (5.9%). Imaging directly contributed to the diagnoses in 20 out of 102 patients (19.6%). In all patients in which imaging contributed to the diagnoses, there were focal signs or symptoms leading the physician to order the image.

There were several differences in the workup of patient with FUO, both by fever duration and by category (Table 4). Children with longer fever duration (>21 days) were more likely to receive a bone scan (15.79%) than those with shorter durations of fever ($P < .01$). Bone scans were more commonly obtained in children with longer fever duration and those with unknown or other when compared with other categories ($P < .01$). Those with final diagnoses of autoimmune and oncologic causes were more likely to undergo ultrasonography (64.3%, $P < .05$ and 61.1%, $P < .01$, respectively). Radiographs were most frequently performed in those with an ultimate oncologic diagnosis (94.4%, $P < .05$).

The laboratory tests obtained, with values organized by length of fever and FUO category, can been found in Supplemental Table 5. Every patient had at least 1 laboratory test performed. A complete blood cell count was the most frequent laboratory test (90.1%), followed by basic metabolic panel (77.5%), liver function tests (62.7%), inflammatory markers (57.8%), lactate dehydrogenase (43.1%), uric acid (37.3%), and ferritin (34.4%). There were no statistically significant differences in laboratory values by length of fever duration; however, there were differences when compared by category. The mean leukocyte count was significantly different based on category, with the highest white blood cell counts in the autoimmune group (21.7 mg/dL) and lowest in the other or unknown group (8.4 mg/dL). Transaminases (aspartate aminotransferase, alanine aminotransferase) were elevated in all categories. The inflammatory markers erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin, but not platelets, were elevated in all categories. There was no difference in CRP values between categories; however, a statistically significant elevation in ESR was noted in the autoimmune and infectious categories when compared with oncologic and other or unknown categories.

Overall, 95.1% of children received a subspecialty consult, with infectious disease being the most common subspecialty involved. There was not a statistically significant difference in frequency of consultation across fever duration or categories.

LOS and Hospital Costs

The average LOS for all children admitted with FUO was 8.6 days with a total mean hospital cost of $48 684.53 (Supplemental Table 6). Children with other or unknown diagnoses had a mean LOS of 5.7 days and infectious diagnoses had mean hospital charges of $40 317. Children with an oncologic diagnosis had increased mean LOS (12.6 days) and mean hospital costs ($75 165) compared with other categories, although these trends did not meet statistical significance ($P = .08$).

DISCUSSION

In this retrospective analysis of a large cohort of children hospitalized with FUO, there are 3 main findings. First, unlike changes in adult FUO, the etiologic categorization of FUO has not markedly changed over the past 3 or 4 decades. Second, our study noted some limited differences in specific diagnoses compared with the 3 sentinel pediatric FUO studies. Third, the distribution of etiologic categories has not been altered substantially by a shortening of the required duration of fever used to define FUO (>7 vs >21 days).

The 3 seminal publications on pediatric FUO in the 1970s revealed the underlying cause of fever could be identified 68% to 88% of the time, and were categorized as 29% to 52% infectious, 11% to 20% autoimmune, 12% to 32% undiagnosed, and 6% to 13% oncologic.[5–7] Smaller studies performed in the 1990s had highly variable findings and noted that up to 67% of FUO remained

TABLE 4 Diagnostic Testing by Length of Fever and Etiology

	Length of Fever					Etiology				
	Total	>8–14 d	>15–21 d	>21 d	*P*	Infectious	Autoimmune	Oncology	Other or Unknown	*P*
Scans (%)										
Radiograph	70.59	66.67	57.89	81.58	.134	59.52	75.00	94.44	64.29	.047
Ultrasound	47.06	44.44	63.16	42.11	.290	35.71	64.29	61.11	28.57	.031
CT	7.84	4.44	5.26	13.16	.304	11.90	3.57	0.00	14.29	.261
MRI	9.80	8.89	5.26	13.16	.616	9.52	10.71	0.00	21.43	.248
Bone scan	5.88	0.00	0.00	15.79	.005	2.38	0.00	5.56	28.57	.001
Cultures (%)										
Blood	80.39	77.78	84.21	81.58	.817	78.57	78.57	88.89	78.57	.801
Urine	46.08	40.00	68.42	42.11	.094	47.62	35.71	55.56	50.00	.575
CSF	23.53	15.56	21.05	34.21	.131	19.05	14.29	44.44	28.57	.095
Fluid culture	14.85	6.67	21.05	21.62	.116	14.63	10.71	11.11	28.57	.446
Positive culture result (%)	0.00	0.00	0.00	0.00	—	0.00	0.00	0.00	0.00	.000
Viral panel (%)	43.14	51.11	36.84	36.84	.352	38.10	57.14	38.89	35.71	.373
Positive viral panel (%)	8.82	8.89	5.26	10.53	.804	11.90	7.14	5.56	7.14	.830

CSF, cerebrospinal fluid; CT, computerized tomography; —, not applicable.

undiagnosed.[8,9] A comparison of categories based on publication year can be found in Fig 1A. Our study is consistent with the original pediatric studies in that an identifiable etiology was found in 86.4% of patients. Overall, the etiologies we identified were 41.2% infectious, 27.5% autoimmune, 17.7% oncologic, and 13.7% other or unknown. The reason for the modest increases in oncologic etiologies compared with previous studies is unclear. Similar to previous studies, we noted a wide variety of causes, with 46 distinct diagnoses in our 102 patients. Our study findings reveal that the underlying etiologies of pediatric FUO also have changed to a limited degree, unlike the changes seen with adult FUO.[2–4]

Although we did find marginal differences in the underlying causes of FUO compared with previous studies, it is worth noting the definition of FUO has changed over time. The original pediatric studies on FUO used a fever duration of 2[7] or 3[5,6] weeks as well as temperatures of 38.3°C,[5] 38.5°C,[7] or 38.9°C.[6] Over the past 3 decades, the fever length and height required for a diagnosis of FUO have changed.[1] Despite our study definition of FUO as a temperature of 38.0°C for >7 days, we did not find a large variation in the causes FUO compared with studies with a FUO duration of 2 or even 3 weeks (Fig 1). It is notable that the causes of FUO have not markedly shifted despite decreasing the required fever, height, and duration.

The diagnoses in our series that were not seen in the 1970s publications include Kawasaki disease, hemophagocytic lymphohistiocytosis and macrophage activation syndrome, diskitis, ehrlichiosis, metapneumovirus, and *Clostridium difficile* colitis. These diseases were undiscovered in the 1970s and their prevalence in our cohort reflects improved diagnosis of previously unknown entities. Furthermore, diseases such as tuberculosis and malaria that were found in the 1970 studies were not identified in our patients, likely reflecting decreasing incidence and improved early detection of these diseases in the United States. A significant portion of diagnoses (~24%) were benign in origin, either viral or unknown etiology that self-resolved. Given that a high proportion of FUO is self-limited, further study is needed on improving the efficiency of FUO diagnostic workup to better predict serious versus benign etiologies.

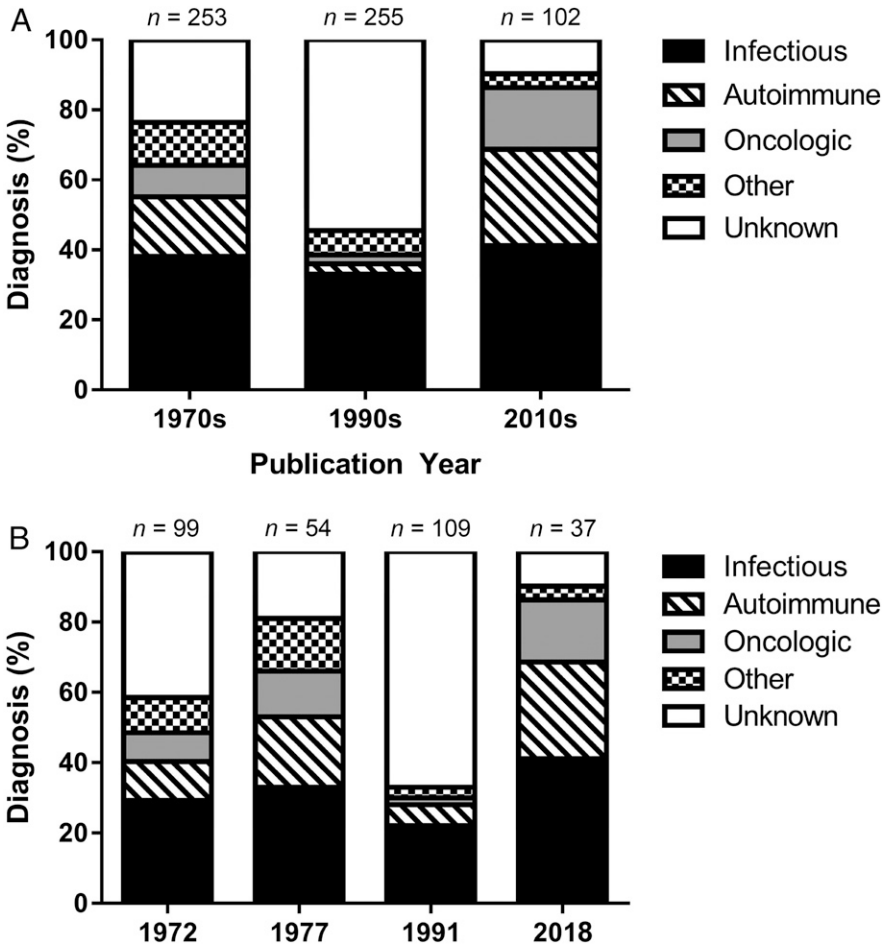

FIGURE 1 A, Evolving etiology of pediatric FUO.[5–9] FUO definitions are as follows: >38.9°C for >21 days (1972), >38.5°C for >14 days (1975), >38.3°C for >21 days (1977), >38.0°C for >21 days (1991), >38.0°C for >14 days (1998), and >38.0° for >7 days (2017). B, Evolving etiology of FUO >3 weeks.[5,6,9] FUO definitions are as follows: >38.9°C for >21 days (1972), >38.3°C for >21 days (1977), >38.0°C for >21 days (1991), and >38.0° for >7 days (2018).

Several notable observations can be made from the laboratory and imaging studies performed. Although infection was the most common cause overall of FUO, and every patient received at least 1 culture, no culture results were reported as positive. There is a growing body of literature on the lack of utility of blood cultures in common inpatient pediatric diseases such as soft tissue infections, urinary tract infections, and pneumonia.[10–12] Our results calls into question the utility of blood, urine, and cerebrospinal fluid cultures in this pediatric FUO population. Furthermore, although acute phase reactants, such as CRP and ferritin, are commonly elevated above normal values, their utility in differentiating between etiologic categories remains limited. This finding may be because of the high sensitivity and low specificity associated with the mild to moderate elevations of either test and the fact that the underlying pathologic mechanisms of most causes of FUO involve activation of the inflammatory cascade.[13–17]

We also found that imaging studies were performed in 100% of cases but rarely led to the final diagnosis. The imaging studies that produced positive results were suggested by physical signs and symptoms rather than being used as screening techniques. Our results support those of Steele et al,[9] who found that imaging and

scanning procedures had positive findings in <25% of cases and did not frequently contribute to FUO diagnosis. Furthermore, although several laboratory studies were consistently abnormal compared with normal values, we found that most laboratory study results were not statistically significantly different between categories, thus not differentiating between FUO etiologic categories. Of note, leukocytes were notably higher in the autoimmune and infectious groups than in the oncology and other or unknown group, likely resulting from the increased inflammatory state involved in autoimmune and infectious disease processes.

FUO evaluation often results in expensive and exhaustive investigative testing. To our knowledge, this study is the first to compare hospital LOS and hospital costs between FUO categories and duration of fever. Hospital LOS was similar in the autoimmune, infectious, and other or unknown categories. The LOS in the oncology category was significantly longer than the other etiologic categories, most likely because of the complicated management and treatment course of this subgroup. Furthermore, hospital costs were higher in the oncology category and the fever duration of 14 to 21 days subgroup. These results confirm the widespread belief that the evaluation of a child with FUO generates considerable expense. However, with our findings, we suggest that although significant resources are used in the diagnostic workup of FUO, there are no compelling data to support broad testing because few nonspecific laboratory studies are highly useful in distinguishing between FUO categories. Taken together, these results reveal that focused testing for FUO is a potential avenue for decreasing resource use and hospital costs.

We recognize there are limitations inherent to this type of retrospective study. First, this is a single-center study and our data may be influenced by local disease prevalence and geographic homogeneity, which may not be generalizable. Second, our study defined FUO as fever of as short a duration as >7 days, which may alter our findings compared with those who use a longer duration of fever. To minimize this effect, we analyzed our findings by 3 different durations of fever. Third, we identified eligible patients on the basis of an admitting diagnosis of fever. It is possible that patients were admitted under a diagnosis other than fever and thus were not captured. Finally, our study is limited to hospitalized patients and may not be fully generalizable to outpatient FUO workups.

CONCLUSIONS

In our study, performed 4 decades after the defining pediatric FUO studies, we demonstrate that the distribution of etiologic categories of FUO have not changed significantly over time. The distribution of etiologies within the categories has not been altered substantially by a shortening of the required duration of fever used to define FUO (>7 vs >21 days). Laboratory studies are commonly obtained but infrequently distinguish between FUO etiologic categories. Our findings call into the question the diagnostic utility of imaging and cultures because these studies did not contribute to the final diagnosis in our FUO population. Pediatric patients hospitalized with FUO undergo a prolonged LOS and generate high hospital costs.

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