Fever of unknown origin in children: a systematic review

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Background: **There are no previous systematic reviews of published pediatric case series describing the etiology of fever of unknown origin (FUO). The purpose of collecting these data is to determine the etiologies for children with FUO in both developing and developed countries.**

Methods: **The database Ovid Medline R (1950 to August 2009 week 4) and Ovid Embase (1980 to 2010 week 2) were used to conduct the search. Studies in any language were included if they provided the diagnosis in a series of 10 or more children with FUO. The diagnosis of each child at the time of publication of the study was recorded.**

Results: **There were 18 studies that met the inclusion criteria, describing 1638 children. The diagnosis at the time of publication was malignancy for 93 children (6%), collagen vascular disease for 150 (9%), miscellaneous non-infectious conditions for 179 (11%), infection for 832 (51%), and no diagnosis for 384 (23%). There were 491 bacterial infections (59% of all infections) with common diagnoses being brucellosis, tuberculosis, and typhoid fever in developing countries, osteomyelitis, tuberculosis, and Bartonellosis in developed countries, and urinary tract infections in both. For children with no diagnosis after investigations, most had fever that ultimately resolved with no sequelae.**

Conclusions: **About half of FUOs in published case series are ultimately shown to be due to infections with collagen vascular disease and malignancy also being common diagnoses. However, there is such a wide variety of possibilities that investigations should primarily be driven by the clinical story.**

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Introduction

Fever of unknown origin (FUO) was firstly described in 1961 and defined as well-documented fever of at least 3 weeks duration with no apparent source after 1 week of investigations.[1] It is now generally accepted that unexplained fever that persists longer than 1 week in a child warrants preliminary investigations as fever from viral infections generally resolves within that time frame. Therefore, most recent case series of pediatric FUO require persistence of fever for only 1 or 2 weeks with negative preliminary investigations, and the investigations required varied by study.

This study summarized the literatures on pediatric FUO to determine the relative incidence of different etiologies, expecting that etiology will vary by geographical location related to the economy of the region, the presence of vectors of infection, and the availability of diagnostic tests.

Methods

Search methods for identification of studies

The database Ovid Medline R (1950 to August 2009 week 4) and Ovid Embase (1980 to 2010 week 2) were used to conduct the search. Key words and phrases used to refine the search included "fever of unknown origin" and "pyrexia of unknown origin", limited to children 0 to 18 years. The search was then further limited to include clinical trials, meta-analysis, epidemiologic studies, evaluation studies, validation studies, review articles, retrospective and prospective studies. All abstracts were then reviewed.

Study characteristics

Studies were included if they provided the diagnosis in a series of 10 or more inpatients or outpatients of less than 18 years of age evaluated for FUO persisting

for a minimum of one week duration. Because one of the goals of the study was to look at the incidence in different geographic areas, no language restriction was applied. Studies were excluded if they included only acute FUO (fever for less than one week) or focused only on long-term follow-up of children with unexplained FUO.

Data extraction

Data were recorded on the demographics and diagnosis at the time of publication for enrolled children. The data were separated for studies from advanced economies (developed countries) versus emerging or developing economies (developing countries) using International Monetary Fund classification from 2008 (Imf-advanced-un-least-developed-2008.svg).

Data analysis

This was purely a descriptive study so it was not possible to report study quality or risk of bias. The etiologies of fever were classified into the following groups: a) infectious diseases, b) malignancy, c) collagen vascular disease (CVD), d) miscellaneous diseases including hemophagocytic lymphohistiocytosis, inflammatory bowel disease, and any other conditions with a proven etiology, and e) no etiology established at the time of publication. Infectious diseases where classified as bacterial, fungal, parasitic, or as infectious syndromes with no specified pathogen.

Results

The search revealed 643 abstracts of which 18 studies met the inclusion criteria (13 in English, 2 in French, 2 in Spanish and 1 in Polish). Six other studies were excluded as they included children up to 21 years of age,[1] the duration of fever was less than 1 week in some children,[2,3] there were less than 10 patients in the study,[4] or the study was limited to children with unexplained FUO following a full evaluation.[5,6] Only the latter two studies provided data on a long-term follow-up of children with FUO. One study looked at children referred to a rheumatology clinic with a mean follow-up of 5 years: 32 of 37 children had resolution of their fever with no diagnosis, 3 had persistent periodic fever, and 2 had a diagnosis of Crohn's disease.[7] Another study from Chicago reported follow-up of 19 children for a mean of 3.5 years after assessment: 16 had resolution of their fever with no established etiology, 2 were eventually diagnosed with juvenile idiopathic arthritis, and 1 had recurrent intussusception that may be due to the initial fever.[6]

The 18 included studies published from 1968 to 2008 consisted of 8 studies (all more than a decade old) from only 3 developed countries (Germany, USA and Spain) and 10 studies from developing countries (Table 1).[8-25] The number of children in each case series varied from 10 to 221 (median 89.5) for a total of 1638 children (770 males; 628 females; 240 unknown). Definitions of FUO varied widely. The values for the definition of fever varied from minimum 37.5 degrees Celsius to minimum 38.9 degrees Celsius. The duration of fever ranged from 1 week to 3 weeks with the majority of the papers requiring a minimum of 2 to 3 weeks duration. In terms of the site of investigation, 1316 children were inpatients during at least part of their investigation, 209 were outpatients and for 113 it was not specified.

The total number of patients with a diagnosis of malignancy was 93 (6%), of which 41 had leukemia, 16 had lymphoma, 23 had other types of malignancy including neuroblastoma, Wilms tumour, and myeolodysplastic syndrome, and 13 had an unspecified malignancy. The number of patients with a diagnosis of collagen vascular disease was 150 (9%), of which 90 had juvenile idiopathic arthritis, 22 had systemic lupus erythematosis, 27 had some other forms of CVD and 11 patients had an unspecified type of CVD. One hundred and seventy-nine patients had a miscellaneous non-infectious etiology for their fever (11%) (Table 2) with nonspecified autoimmune disease and inflammatory bowel disease predominating in developing countries and Kawasaki disease in developed countries.

Infection was by far the most commonly identified etiology of FUO in all studies. In total, 832 patients (51%) had a final diagnosis of infection with bacterial infections followed by infectious syndromes being the most common etiologies. There were 491 bacterial infections (59% of all infections) with common diagnoses of brucellosis, tuberculosis, and typhoid fever in developing countries, osteomyelitis, tuberculosis, and Bartonellosis in developed countries, and urinary tract infections in both (Table 3). There were 58 patients with viral infections (7% of all infections) with Epstein-Barr virus (EBV) accounting for over half of cases. Another 193 patients (23% of those with infections) had infectious syndromes associated with pneumonia accounting for fully one-quarter of these in developing countries. Fungal infection was diagnosed in only 3 of the 832 patients, but 86 had parasitic infections (10%), predominantly leishmaniasis in developing countries.

Table 1. Case series of fever of unknown etiology in children, divided into developed and developing countries and listed in order of the year of publication

Study (country, year of publication)	Definition of fever of unknown origin	*n*	Malignancy	Collagen vascular diseases	Miscellaneous non-infectious diagnosis	Infection	No diagnosis at time of publication
Developed countries							
Germany 1998[8]	Fever >39°C, WBC ≥15×10^3/μL, duration of fever minimum 2 weeks and with minimum 1 week of inpatient evaluation	30	0	5 (17%)	5 (17%)	15 (50%)	5 (17%)
USA 1998[9]	Documented daily fever ≥38 °C for at least 14 days without diagnostic signs or symtoms	146	4 (3%)	0	16 (11%)	64 (44%)	62 (42%)
Spain 1994[10]	Fever >1 week with rectal temperatures >38.5°C	32	1 (3%)	7 (22%)	0	23 (72%)	1 (3%)
USA 1991[11]	Fever ≥38°C at least twice a week for ≥3 weeks with a normal urinalysis and chest X-ray	109	2 (2%)	8 (7%)	4 (4%)	22 (20%)	73 (67%)
Spain 1978[12]	Rectal temperature >38.9°C on multiple occasions for minimum 3 weeks outpatient evaluation or minimum 1 week of inpatient evaluation	79	10 (13%)	7 (9%)	3 (4%)	52 (66%)	7 (9%)
USA 1977[13]	Fever >38.3 °C with unknown souce after 3 weeks evaluation as an oupatient or 1 week inpatient evaluation	54	7 (13%)	8 (15%)	11 (20%)	18 (33%)	10 (19%)
USA 1975[14]	Rectal temperature >38.5°C on >4 occasions for at least a 2 week period	100	6 (6%)	16 (16%)	14 (14%)	52 (52%)	12 (12%)
USA 1972[15]	Rectal temperature >38.9°C for a minimum of 3 weeks outpatient evaluation or minimum 1 week of inpatient evaluation	99	8 (8%)	11 (11%)	19 (19%)	29 (29%)	32 (32%)
Total – developed countries		649	38 (6%)	62 (10%)	72 (11%)	275 (42%)	202 (31%)
Developing countries							
India 2008[16]	Fever >2 weeks with unknown source after history, physical exam, and screening lab tests	49	6 (12%)	1 (2%)	2 (4%)	34 (69%)	6 (12%)
Poland 2007[17]	Rectal temperature >38.3°C for duration of 3 weeks with no source on initial investigation	10	0	0	5 (50%)	5 (10%)	0
Tunisia 2006[18]	Fever >17 days for kids between 2 and 15 yrs	110	3 (3%)	8 (7%)	9 (8%)	64 (58%)	26 (24%)
Serbia 2006[19]	Fever >3 weeks with temperature >38.3°C & no diagnostic signs or symptoms	185	12 (6%)	24 (12%)	25 (14%)	70 (38%)	54 (29%)
Georgia 2006[20]	Fever >38°C for at least 3 days per week, lasting for more than 3 weeks and failure to diagnoze using complete blood count, urinalysis and chest X-ray	52	2 (4%)	2 (4%)	1 (2%)	40 (77%)	7 (13%)
Tunisia 2004[21]	Fever for 2 weeks with unknown source	67	2 (3%)	14 (21%)	0	38 (57%)	13 (19%)
Turkey 2003[22]	Fever >37.5°C for greater than 2 weeks with an unknown source	80	2 (3%)	5 (6%)	16 (20%)	47 (59%)	10 (13%)
Turkey 2003[23]	Fever >38.3°C for minimum of 3 weeks after 1 week intensive investigation	102	12 (12%)	7 (7%)	26 (25%)	45 (44%)	12 (12%)
Argentina 1994[24]	Fever ≥38.3°C for at least 3 weeks including 1 week of intensive investigation	113	11 (10%)	16 (14%)	23 (20%)	41 (36%)	22 (19%)
Kuwait 1990[25]	Rectal temperature ≥38.3 for a minimum 2 weeks as an outpatient or >1 week investigation as an inpatient	221	5 (2%)	11 (5%)	0	173 (78%)	32 (14%)
Total – developing countries		989	55 (6%)	88 (9%)	107 (11%)	557 (56%)	182 (18%)
Total – all countries		1638	93 (6%)	150 (9%)	179 (11%)	832 (51%)	384 (23%)

Table 2. Miscellaneous diagnoses in children with fever of unknown origin

Miscellaneous diagnosis	Developed countries*	Developing countries†
Autoimmune, non-specified	11	0
Drug-induced	7	1
Toxins	2	0
Inflammatory bowel disease	12	6
Kawasaki disease	0	27
Factitious fever	2	9
Hemophagocytic syndrome	0	10
Immunodeficiency	1	9
Familial mediterranean fever	0	10
Others	37	35
Total	72	107

*: USA, Germany, and Spain; †: Tunisia, India, Turkey, Poland, Argentina, Serbia, Georgia, and Kuwait.

In total, 384 patients had FUO with no diagnosis at the time of publication (23%). Resolution of fever by the time of publication in the absence of a diagnosis was reported in 190 of these 384 patients (49%). Another 25 patients had persisting fever, while the outcome was not reported for the remaining 169 patients.

Other than differences in the types of infections as outlined above, the distribution of etiologies was similar in developed versus developing countries.

Discussion

In the published case series, just over half of cases

Table 3. Infectious etiologies identified in children with fever of unknown origin

Infectious etiologies	Developed countries*	Developing countries†	Total
Bacterial infections			
Brucellosis	7	97	104
Urinary tract infection	21	40	61
Tuberculosis	22	39	61
Typhoid fever	7	47	54
Abscess	3	33	36
Septicemia	9	23	32
Osteomyelitis	25	4	29
Endocarditis	6	14	20
Pyelonephritis	11	8	19
Bartonellosis	10	5	15
Rickettsiae	0	12	12
Mycoplasma	0	4	4
Lyme disease	2	0	2
Others	30	12	42
Total bacterial	153	338	491
Viral Infections			
EBV	31	7	38
Enterovirus	4	0	4
CMV	4	3	7
HIV	1	2	3
HSV	1	2	3
Hepatitis	1	2	3
Total viral	42	16	58
Infectious syndromes			
Pneumonia	16	32	48
Respiratory non-specified	6	32	38
Viral syndromes non-specified	17	12	29
Infectious mononucleosis	5	18	23
Meningitis	9	9	18
Sinusitis	7	3	10
Encephalitis	2	0	2
Others	9	16	25
Total infectious syndromes	71	122	193
Fungal infections			
Blastomycosis	1	0	1
Histoplasmosis	1	0	1
Fungal non-specified	0	1	1
Total fungal	2	1	3
Parasitic infections			
Leishmaniasis	5	61	66
Malaria	1	10	11
Infected hydatid cysts	1	6	7
Toxoplasmosis	0	2	2
Total parasitic	7	79	86
Unknown infections	0	1	1
Total infections	275	557	832

*: USA, Germany, and Spain; †: Tunisia, India, Turkey, Poland, Argentina, Serbia, Georgia, and Kuwait. EBV: Epstein-Barr virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus; HSV: herpes simplex virus.

if FUO in children are eventually proven to be from infectious diseases. The majority of these infections are bacterial in origin. A wide variety of malignancies and CVDs account for 6% and 9% of cases respectively, while a broad range of miscellaneous non-infectious diagnoses comprise 11% of cases. About one-quarter of cases never have an established diagnosis, and it appears the majority of these children eventually have resolution of the fever.

When comparing data between developed and developing nations, infection is consistently the most common cause of FUO but the types of infections vary. With regards to bacterial infections, Bartonella infections were more commonly diagnosed in developed countries while brucellosis, typhoid fever, tuberculosis, rickettsial infections, and abscesses were more common in the developing nations. Viral etiologies for FUO were more commonly identified in the developed countries, particularly EBV. When looking at infectious syndromes, pneumonia was far more common in developing nations, presumably as diagnosis can be delayed because of poor access to oximetry or a chest radiography. Some of the differences are undoubtedly related to a higher incidence of infections such as tuberculosis or parasitic disease in developing countries but other differences may relate more to the availability of diagnostic tests.

The main limitation of the current study is that the published case series of FUO over the decades may not be representative of FUO in general in 2010. There is no reliable way to judge the quality of the heterogeneous descriptive studies included in this review. The data are biased by inclusion of only limited geographic areas in the 18 studies with only one study from each of Asia, Africa, and South America. It is difficult to know if this is because clinicians from these continents did not submit manuscripts or because of publication bias favoring studies from North America and Europe. Some conditions such as Kawasaki disease were not yet recognized when the earliest studies were conducted while criteria for other diagnoses and the sensitivity of diagnostic tests changed over time. The incidence of vaccine-preventable diseases will have decreased in some countries. Many of the cases classified as "autoimmune" in older studies were likely CVDs. Furthermore, the definition of FUO varied widely in the studies, and even were it uniform, the etiology of FUO for minimum one week likely differs from that of FUO for minimum three weeks. It is disappointing that long-term outcome data are not available for the large number of children who had no diagnosis established for their FUO. This review did not look specifically at nonclassic FUO (nosocomial, human immunodeficiency virus related, or FUO in the immunocompromised host).[26]

A recent study from Greece demonstrated that over 85% of adults with FUO had infection if they had two of the following: 1) serum ferritin <500 μg/L; 2) eosinophils <40/mm^3; and 3) C-reactive protein >60

mg/L.[27] There is a great need for large prospective pediatric studies in developed and developing countries, ideally validating this simple predictive scheme and testing an algorithm for management.

Based on the current study, limited investigations should be performed routinely in previously well children with FUO since the differential diagnosis is so extensive. Early diagnosis of malignancy can improve the prognosis so a complete blood count and differention would appear to be indicated. Blood cultures would be most useful in children with FUO in developing countries to rule out typhoid fever, brucellosis or "septicemia" but should also be performed in developed countries to rule out serious treatable infections such as infective endocarditis. If available, serology for EBV should also be considered with the initial work-up as EBV is the most common viral etiology of FUO. Furthermore, most laboratories save serology samples for months, which may prove useful if acute and convalescent serologies are later deemed to be useful for another infection. Based on the relatively high incidence of urinary tract infections and pneumonia in all settings, all patients should have a urine culture and a chest radiograph performed. A tuberculosis skin test should be ordered if the patient has any tuberculosis risk factors. Other investigations for infections such as leishmaniasis should be considered in endemic regions. Other tests suggested for the initial assessment in a 2001 review include serum protein electrophoresis, blood film examination, erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibodies, and antistreptolysin O antibodies followed by bone marrow examination if no diagnosis had been made.[28] A 2010 review also suggested a comprehensive metabolic profile including uric acid and lactate dehydrogenase and quantitative serum immunoglobulins.[26] If initial investigations are not diagnostic but the patient seems relatively well when afebrile, it would be logical to follow the patient closely and order further investigations as indicated by new signs or symptoms. Given the wide variety of possible etiologies, empiric antibiotics should be avoided unless there is a high index of suspicion for an untreated serious bacterial infection.

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