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ORIGINAL ARTICLE

FEVER OF UNKNOWN ORIGIN IN CHILDREN: A FIVE-YEAR REVIEW

ABSTRACT

Objectives: The clinical presentation, outcome, and risk factors for mortality in children with Fever of Unknown Origin (FUO) were determined.

Methods: Medical records of pediatric patients admitted for FUO from January 2009 to December 2013 were reviewed. Clinical manifestations, physical exam findings, diagnostic work-ups and final diagnosis were determined, as well as the relationship between final diagnosis and risk for mortality.

Results: Fifty-seven patients with FUO were included. Weight loss, cough, colds, and rashes were common symptoms while pallor, lymphadenopathies, and hepatomegaly were common physical exam findings. All patients underwent Phase I evaluation for FUO, while 73.7% underwent further diagnostic tests. A specific etiology was established in 96.5% of cases: infectious, 43.9%, connective tissue disease, 38.6%, and hematologic/oncologic, 14%. Two cases remained to have no specific diagnosis. Majority of patients had a benign course and were discharged improved (84.2%). The mortality rate is 15.8% and was not associated with any disease category (p-value 0.204).

Conclusions: FUO in children occurs across all age groups. Its clinical presentations are varied and non-specific and common signs and symptoms are pallor, lymphadenopathies, weight loss, cough, colds. and joints pains. Infection is the most common cause of FUO in children, followed by connective tissue diseases and hematologic and oncologic diseases. The mortality rate from FUO is 15.8%.

KEYWORDS:
Fever of unknown origin, FUO,

INTRODUCTION

Fever is a common constitutional symptom due to a wide array of health conditions. The occurrence of fever in children poses a challenge to pediatricians in daily clinical practice.[1] A prolonged and persistent course with undetermined etiology adds further to the dilemma.[2]

Fever of unknown origin (FUO) is defined as a temperature greater than 38°C documented by a health care provider for which the cause is unidentified after three weeks of outpatient evaluation or after one week of hospital admission.[1] Despite current advances in medicine, there is still no universally acceptable guideline on diagnosis and management of FUO as far as the extent of evaluation, indications for hospital admission, and use of empiric antibiotics are concerned.[2] The Philippine Pediatric Society in 2004 presented phases of diagnostic testing as a guide in evaluating children with FUO. Phase I includes tests such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), urinalysis, Tuberculin skin test (TST), chest x-ray, blood culture and ASO titer. Phase II includes lumbar puncture, repeat blood culture, sinus and mastoid x-rays, serologic tests such as those for Human Immunodeficiency Virus (HIV), Salmonellosis, Brucellosis, Tularemia, Epstein Barr Virus, Cytomegalovirus, Toxoplasmosis, Hepatitis, Fungal infection, and Malaria smear, and liver function tests such as, aspartate transaminase (AST), and alanine transaminase (ALT). Phase III includes abdominal ultrasound, abdominal CT scan, upper GI series, bone marrow aspiration and bone scanning.[3]

At present, there is limited local data on FUO in children. This study aims to determine the presentation, outcome and risk factors for mortality of pediatric patients with FUO admitted under the Department of Pediatrics of the Philippine General Hospital, a tertiary government hospital, from January 2009 to December 2013.

METHODS

This is a retrospective study where data was obtained through review of patient medical records.

Patients 0-18 years old admitted for FUO at the pediatric emergency room, pay and charity wards of the Philippine General Hospital from January 2009 to December 2013 were included.

Patients with known acquired or congenital immunodeficiencies and those FUO patients with incomplete data on the medical records were excluded.

Admission registry logbooks at the Pediatric Emergency Room were reviewed. All patients seen from January 2009 to December 2013 with a chief complaint of prolonged and/or persistent fever documented by a health care provider with unidentifiable cause after 3 weeks of outpatient evaluation and those from other hospitals admitted for more than 1 week for which the cause of fever is still unknown were included. Medical charts of patients who fulfilled the criteria for FUO were retrieved and reviewed for completeness. Complete charts are those with the following information: case number, date of admission, name, age, sex, onset of fever, fever pattern, accompanying signs and symptoms, documented diagnostic evaluation and results, medications, procedures done and final diagnosis. Incomplete charts were excluded.

Specific clinical outcomes (discharged improved, not improved, died) were recorded. Additional data of discharged patients seen on follow-up were also noted based on their outpatient medical records.

Descriptive statistics were used to summarize the data presented as frequencies and proportions or percentages. To analyze the association

between the final etiologic diagnosis for FUO (infectious versus non-infectious causes) and mortality, odds ratios were determined and a p-value of <0.05 was considered statistically significant.

RESULTS

One hundred two cases with an admitting impression of FUO, prolonged fever or persistent fever were identified from the pediatric ER triage logbook. Of these, 59 charts were retrieved from the medical records section. Two charts were incomplete and were excluded. Fifty-seven charts were included in the final analysis.

Table 1 shows the age and sex distribution of patients admitted for FUO. The majority were below 10 years old, with the highest number of cases in the 6 to 9 years old age group. There was a slight female predominance with a ratio of 1.2:1.

Table 1. Age and sex distribution of patients with FUO.

Age (in years)	Male		Female		Total	%
	Number	%	Number	%		
0-2	7	12.3	3	5.3	10	17.5
3-5	5	8.8	6	10.5	11	19.3
6-9	7	12.3	8	14.0	15	26.4
10-14	4	7.0	7	12.3	11	19.3
15-18	3	5.3	7	12.3	10	17.5
Total	26	45.6	31	54.4	57	100

The duration of fever before ER admission ranged from 14 to 281 days with a mean duration of 64 days). The highest temperature recorded was 41°C (mean 39.45°C ±0.64). Most patients presented with intermittent fever (61.4%). Accompanying signs and symptoms varied but the most common symptoms were weight loss (71.9%), cough and colds (52.6%), and joint pains or arthralgia (40.3%). Most common signs were pallor (50.9%), lymphadenopathies (24.6%) and hepatomegaly (10.5%). (Table 2)

SYMPTOMS	Number of Patients (n=57)	Percentage
SYMPTOMS		
Weight loss	41	71.9%
Cough/colds	30	52.6%
Arthralgia	23	40.3%
Rashes	22	38.6%
Abdominal pain	21	36.8%
Anorexia	18	31.6%
Body malaise	18	31.6%
Vomiting	15	26.3%
Headache	14	24.6%
SIGNS		
Pallor	29	50.9%
Lymphadenopathies	14	24.6%
Hepatomegaly	6	10.5%
Bleeding	4	7.0%

Table 2. Signs and symptoms of FUO in

Of the 57 cases, 26.3% had a definite diagnosis after Phase I evaluation, 24.6% needed to undergo Phase II tests, but most cases (49.1%) required Phase III evaluation before a definite diagnosis could be made. Among the 28 who underwent Phase III evaluation, two patients (3.5%) still had no diagnosis until the time of discharge.

Initial laboratory findings of FUO patients are shown in Table 3. More than 50% of cases showed normal white blood cell (WBC) counts, while 38.6% presented with leukocytosis. Urinalysis was normal in the majority, as with chest radiographs in 42.1% of cases. Of the 21 patients where a tuberculin skin test (TST) was performed 7 had a reading of ≥10mm in duration and had TB as a diagnosis. Three patients where the TST reading was <10 mm turned out to be TB cases after additional work-ups.

Table 3. Laboratory Findings in Patients with FUO.

Parameter	Number of Cases	Percentage
White Blood Cell (WBC) count (n=*57*)		
5000 to 10,000 x10^{9}g/L	30	52.6%
>10,000 x10^9/L	22	38.5%
<5000 x10^9/L	5	8.7%
Urinalysis (n=*53*)		
WBC <10/hpf	30	56.6%
WBC ≥10/hpf	23	43.3%
ESR (n=23)		
≥ 20 mm/hr	8	34.7%
< 20 mm/hr	15	65.2%
CRP (*n= 21*)		
<6 units	7	33.3%
≥6 units	14	66.6%
Chest x-ray (*n= 50*)		
Normal	28	56%
pneumonia	12	24%
hilar lymphadenopathies	8	16%
pleural effusion	2	4%
TST reading (*n=21*)		
≥10mm	7	33.3%
<10mm	12	57.1.0%
unknown	2	9.5%

Table 4 lists the final diagnosis following in-patient diagnostic evaluation. The final diagnoses of most of pediatric FUO cases were infectious in etiology (43.9%) with TB (19.3%), and typhoid fever (10.4%) as the leading causes. Twenty cases were diagnosed to have connective tissue diseases (38.6%), and the majority were identified to have Systemic Lupus Erythematosus (SLE), (17.5%) or Juvenile Idiopathic Arthritis (JIA), (14%). Eight cases (14%) were due to hematologic or oncologic causes, of which acute lymphoblastic leukemia was the most common (10.4%). Two cases (3.5%) remained undiagnosed despite Phase III diagnostic evaluation. In both cases, tuberculosis vs malignancy was considered.

Table 4. Final Diagnosis of Patients with FUO.

Final Diagnosis	Number of Cases	Percentage
I. INFECTIOUS DISEASES	**25**	**43.9**
Tuberculosis	11	19.3
Typhoid Fever	6	10.4
Deep-seated abscess	3	5.3
Complicated pneumonia	2	3.5
Cryptococcal meningitis	1	1.8
Bacterial meningitis	1	1.8
Chronic Pyelonephritis	1	1.8
II. MALIGNANCY	**8**	**14.0**
Acute Lymphoblastic Leukemia	6	10.4
Acute Myelogenous Leukemia	1	1.8
Basal Cell Carcinoma	1	1.8
III. CONNECTIVE TISSUE DISEASES	**22**	**38.6**
Systemic Lupus Erythematosus (SLE)	10	17.5
Juvenile Idiopathic Arthritis (JIA)	8	14.0
Rheumatic Fever	2	3.5
Henoch Schonlein Purpura	2	3.5
Polyarteritis Nodosa	1	1.8
IV. UNDETERMINED	**2**	**3.5**

The duration of hospital stay was shortest in those diagnosed to have an infectious disease as the etiology for the fever, ranging from 5 to 47 days (mean 10.7 ± 8.11 days). Oncologic cases stayed longer, from 11 to 45 days (mean 18.1 ±13.2 days), while those with connective tissue diseases stayed from 6 to 53 days (mean 12.5 ±10.9 days). The 2 cases which remained undiagnosed had the longest hospital stay, 22 and 46 days respectively (mean 34 ±31.1 days).

The outcome of the 57 patients with FUO was generally good, despite the occurrence of 9 deaths (15.8%). The highest mortality was seen in those

with connective tissue diseases, all of whom were diagnosed to have SLE. Of those with infection as the cause, 23 (92%) were discharged improved with only 2 (8%) mortalities due to sepsis.

Table 5 shows that none of the following risk factors: age, sex, duration of fever before admission, maximum temperature, and presenting symptoms, was a significant predictor of mortality with all the p-values exceeding the level of significance of 0.05

Table 6 shows that the probability of dying from FUO due to a connective tissue disease was 2.5 times greater compared to the other disease categories. However, this was not statistically significant (p= 0.441). The overall p-value of 0.204 signifies that the risk of mortality is not associated with any of the three disease categories.

Table 5. Risk Factors for Mortality among FUO Patients.

Possible Risk Factors	Coefficient	Odds Ratio	p-value
Demographic data			
Gender	1.946	7.000	0.078
Age	-0.572	0.564	0.326
Duration of fever prior to admission	0.038	1.039	0.475
Maximum temperature	-0.016	0.984	0.886
Symptoms			
Weight Loss	-	-	0.998
Headache	-0.900	0.407	0.420
Abdominal Pain	-0.188	0.829	0.811
Vomiting	-0.154	0.857	0.860
Rashes	1.265	3.542	0.110
Watery Stools	0.717	2.048	0.432
Joint pains	0.243	1.275	0.759
Generalized Weakness	0.152	1.165	0.847

Table 6. Relationship between disease category and mortality.

	Coefficient	Odds Ratio	p-value
Disease Category			**0.204**
Infectious Disease	-0.657	0.519	0.612
Connective Tissue Disease	0.916	2.500	0.441
Malignancy	-0.946	0.430	0.069

DISCUSSION

Majority of children with FUO seek consult for generalized systemic complaints which makes diagnosis difficult. Uncommon presentations of common diseases were observed in related FUO studies. Constitutional signs and symptoms including fever may persist independently for weeks or months. Therefore, a thorough and organized approach to diagnose cases of prolonged fever is of great importance. Patience, persistence, repeated history taking, physical examination and continued monitoring offer the best chance of making a diagnosis in difficult cases.[4]

The American College of Emergency Physicians recommends that the initial diagnostic tests for FUO should include only CBC, urinalysis, blood culture, and tuberculin skin testing.[5] However, a study done by Simon and colleagues showed that more than 50% of physicians in the United States emergency departments ordered for rapid microbial testing and radiographs for patients presenting in the emergency room.[6] This practice is attributed to changes in the epidemiology and severity of bacterial infections as a result of widespread vaccination, as well as changes in physicians' clinical judgment over time.[5]

The extent of laboratory investigation is dependent on the clinical history, physical examination, age of the patient and duration of fever. A complete blood count, urinalysis and chest x-ray are usually performed as part of the outpatient work-up prior to admission.[7]

Laboratory findings such as elevated leukocyte counts suggest an infectious etiology in patients with FUO.[8] However, in this study, majority of patients had normal leukocyte counts even in those with infection as the cause for the fever. Levels of erythrocyte sedimentation rate (ESR) brought by an increase in hepatic synthesis of fibrinogen, as well as other acute phase reactants such as C-reactive protein (CRP), are of no specific value for they are general indicators of an inflammatory process.[9] In this study, 32% to 37% of patients had elevated ESR and an abnormal CRP which necessitated further investigation. Radiographic examination of the chest was routinely done on all FUO patients as part of the initial workup. Majority of patients in this study had normal chest x-rays and only a few were diagnosed to have complicated pneumonia presenting as lobar consolidation, bronchiectasis or pleural effusion. Tuberculin skin testing (TST) is recommended as an initial test among patients with FUO. Guidelines set by the WHO on the interpretation of the TST stated that a positive TST has an induration of greater than or equal to 10mm in all children whether they have received BCG vaccination or not, as well as an induration of greater than or equal to 5mm in immunocompromised individuals (such as HIV-infected children and those who are severely malnourished).[10] In this study, only 7 out of 11 diagnosed TB cases turned out to be TST positive. Three cases with negative tests were eventually diagnosed to have TB after additional invasive procedures (pleural fluid TB culture, bone biopsy, and liver biopsy).

In this study, infectious diseases were the most common causes of FUO, seen in 25 cases (43.9%), with tuberculosis and typhoid fever as the most frequent infectious etiologies. This supports local and foreign studies on FUO[11,12,13,14,15,16] Infections, therefore, should be considered first because of its frequency and therapeutic implications. Connective tissue diseases, mainly SLE and JIA ranked as the 2nd most common causes, seen in 22 patients (38.6%). This is also noted in other studies on FUO conducted abroad.[15,17] Locally, several descriptive studies in different tertiary hospitals showed that the primary etiology of FUO is infection.[8,11,12] Other causes identified were malignancy, connective tissue disorders or no identifiable etiology, similar to those reported in other studies abroad.[9,13,14,15,16] Although there was a high incidence of infection as the cause for FUO in children, the type of infection differed in developed countries compared those in less developed or developing countries.[7,14,17,18] In a systematic review by Chow and colleagues of 18 published studies on FUO across all countries, they reported that the most common infections were typhoid fever, tuberculosis, and brucellosis in developing countries, while osteomyelitis, bartonellosis, and tuberculosis were the most common in developed countries.[15]

Malignancy as the cause of FUO was determined in 14% of cases and the most identified cases were acute leukemia. Just like infections, malignancy has the ability to produce endogenous pyrogens, such as tumor necrosis factor, which is capable of inducing fever both by acting directly on the thalamus and by stimulating other endogenous pyrogens. In patients with neoplastic disease, the tumor necrosis factor is synthesized and secreted continuously by malignant cells.[1]

In the case review of Lohr and Hendly, neither the pattern of fever nor its duration was useful in establishing a diagnosis in children with

FUO.[9] Most children in this study presented with intermittent fever, however, no particular fever pattern was specific for any of the disease categories. Aside from prolonged fever, accompanying signs and symptoms of patients were generally non-specific, and none were predominantly seen in a specific disease category.

Patients with infection had the shortest duration of hospital stay, with a mean of 10.7 days. These were also the patients who were diagnosed early. On the other hand, the performance of more extensive laboratory work-ups required in the diagnosis of connective tissue and neoplastic diseases have in a way contributed to the prolonged hospital stay of the other patients. Some tests also needed to be sent out to other hospital facilities due to unavailability of such in the hospital laboratory. These tests included ANA, anti-dsDNA, and bone marrow aspiration and biopsy studies.

Tezer and co-authors pointed out in their study that inappropriate use of antimicrobials is a major cause of diagnostic delay.[16] Prior antimicrobial use inhibits the isolation and growth of microorganisms in cultures and prevents seroconversion in diseases such as enteric fever and salmonellosis.[15] In this study, most of the patients were prescribed with various medications from previous consults. Seventy-eight percent had a history of at least 2 antimicrobial courses prior to transfer to our institution. Persistence of fever despite compliance to treatment was the primary reason for transfer for multispecialty/tertiary care. This implies that indiscriminate use of antibiotics for FUO offers no diagnostic or therapeutic benefit and may further obscure the diagnosis.[11] However there are situations where it may be prudent to start empiric antibiotic therapy pending results of diagnostic tests, such as in cases where infection is the primary consideration. Failure to start early and appropriate antibiotic treatment could lead to fatal results.[7] Hence, when a serious infectious disease is suspected, timely investigation, including collection of appropriate specimens for microbiological tests should be conducted prior to empiric antibiotic therapy. Judicious use of antibiotics should be based on the clinical history, physical findings, local epidemiology of disease and suspected etiologic agent.[7]

Children with FUO have a better prognosis since they are less likely to have malignancies or autoimmune processes as the causes of prolonged fever.[7] In this study, FUO patients generally had a benign course and improvement was seen after treatment in 96.5% of cases. In two cases, FUO was suspected to be either due to malignancy or tuberculosis but remained undetermined despite thorough investigation. Both remained stable and were sent home after they were afebrile for more than 48 hours, and even prior to the release of the liver and bone marrow biopsy results. Further diagnostic work up was planned in the outpatient clinic but was not done because they were eventually lost to follow-up. In the study of Velarde, 8% of cases remained undiagnosed but were discharged afebrile and stable.[11] In foreign studies, 10-20% of cases remained undiagnosed despite prolonged work up.[6,16]

Mortality rate was reported at 15.8% in this study and was not associated with any of the disease categories (p-value 0.204). Although the risk of dying was 2.5 times greater in those diagnosed to have a connective tissue disease with 6 of 9 deaths (66.7%), this was not shown to be statistically significant, but could probably be due to the small sample size. Age, gender and presenting signs and symptoms were not shown to predict adverse outcomes.

In a study done among adult FUO patients in 2014, the mortality rate was reported at 6.9%, of which 60% were due to malignancy, specifically Non-Hodgkin's lymphoma. All 164 patients whose

diagnosis remained undetermined at the time of discharge survived. Factors associated with mortality were diagnosis of malignancy, age, continuous (as opposed to episodic) fever, anemia, leucopenia, LDH levels, and hepatomegaly.[19]

Limitations of this study include a considerable number of missing charts, with a retrieval rate of only 57.8%. Other problems encountered were missing results of diagnostic tests done during admission such as x-rays, urinalysis, CRP, ESR, ultrasound, and biopsy, which may have affected the findings in relation to the variables evaluated in the study.

Although a larger sample size might generate different results as to the true number of cases in each of the disease categories as well as the definite diagnosis, this study showed comparable results with similarly conducted studies.

CONCLUSION

Fever of unknown origin in children occurs across all age groups, with the majority of cases occurring in those 6-9 years of age. Clinical presentations are varied and non-specific. The most common symptoms were weight loss, cough and colds, and joint pains, while most common signs were pallor, lymphadenopathies, and hepatomegaly. The most common cause of FUO in children is infection with TB as the most common cause. This is followed by connective tissue diseases and hematologic or oncologic conditions. Mortality rate was 15.8% with the majority of deaths attributed to connective tissue diseases. None of the disease categories were found to be significantly associated with mortality.

RECOMMENDATION

Although this study reflects the findings of other studies done locally and abroad, a multicenter prospective study to determine the clinical profile and outcome of pediatric FUO cases in the Philippines will be more helpful in generating statistically significant outcomes and robust conclusions. Results of larger studies will also help in formulating concise diagnostic and management guidelines for FUO in children.

REFERENCES

1. Nield LS, Kamat D. Fever without a Focus. Kleigman RM, et.al, editors. Nelson Textbook of Pediatrics. 19th edition, Singapore: Saunders Elsevier; 2011. p.896-902.
2. Palazzi D. Fever of unknown origin. Feigin RD, et.al, editors. Textbook of Pediatric Infectious Diseases. 7th edition. Philadelphia: Saunders Elsevier; 2009. p.837-848.
3. Bibera GLG. Infectious causes of FUO. Proceedings of the 41st Annual Philippine Pediatric Society 2004;42-45.
4. Moffet HL. Pediatric Infectious Diseases. 4th edition. Philadelphia, JB Lippincott Company; 1975. p.333-339.
5. Marmor A. Approach to Pediatric Fever with Unknown Source. JAMA. 2007; 298: 2895-904.
6. Simon A, Lukacs S, Mendola P. Emergency Department Laboratory Evaluations of Fever without Source in Children 3 to 36 months. Pediatrics 2011; 128:1368-1375.
7. Talano JA, Katz B. Long Term Follow up of Children with Fever of Unknown Origin. Clin Peds 2000; 39:715-717.
8. Firmalo L, Limchiu D, Tan V, Panahon F, Geronimo G. Prolonged Fever in a Pediatric Setting. Phil J Pediatrics 1983
9. Lohr JA, Hendley JO. Prolonged fever of unknown origin. A record of experiences with 54 childhood patients. Clin Pediatr 1977; 16: 768-773.
10. WHO Guidance for National Tuberculosis Programmes on the management of Tuberculosis in children. 2nd edition, WHO Pres: Geneva, Switzerland; 2014. p.28-29.
11. Velarde M, De Castro JA, Soriano R. Fever of Unknown Origin in Pediatric Patients: A 13-year review at PCMC. Phil J Pediatrics 1995; 44: 30-34, 32:113-116.
12. Campo, MB, Aguirre,C. Fever of Unknown Origin in Children: A Five Year Retrospective Study at The Medical City (unpublished).
13. Arnow,P, Flaherty,J. Fever of Unknown Origin. Lancet 1997; 350: 575-580.
14. Miller L, Sisson B, Tucker L, Schaller J. Prolonged Fevers of unknown origin in children: Patterns of presentation and outcome. J Pediatrics, 1996; 129 (3); 419-423.
15. Chow A, Robinson J. Fever of Unknown Origin in Children. World J Pediatr 2011;7(1):5- 10.

16. Tezer H, Ceyhan M, Kara T, Cengiz AB, Devrim I, Secmer G. Fever of Unknown Origin in children: the experience of One center in Turkey. Turkish J Ped 2012; 54: 583-589.
17. Taweewong, et al. Approach and Management of Fever of Unknown Origin. Vajira Med J 2006; 50 : 203 – 213.
18. Al-Fifi SH. Fever of Unknown Origin: A Case Report. Saudi Med J 2003; 24 (4): 400-402.
19. Vanderschueren S, Eyckmans T, De Munter P, Knockaert D. Mortality in patients presenting with fever of unknown origin. Acta Clin Belg. 2014; 69(1):12-6.