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Original Article

Fever of Unknown Origin at A Tertiary Care Teaching Hospital in Bangladesh

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Elias Bhuiyan[1*], Rahima Sultan[2], Khondoker Ehsanul Arefin[3], Tasmia Islam[4], Fatema khanam[5]

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*Corresponding Author

ABSTRACT

Introduction*: The aim of this study was to determine the causes of fever of unknown origin (FUO) at a tertiary care teaching hospital in Bangladesh.* ***Methods & Materials:*** *A cross-sectional descriptive study was conducted at the Department of Medicine, Bangladesh Medical College Hospital, Dhaka, Bangladesh from January 2021 to December 2023. We reviewed the medical records of all patients aged > 18 years with a primary diagnosis of PUO. We excluded those who did not meet inclusion criteria.* ***Results:*** *One hundred twenty patients were analyzed, 111 (54%) were male. The mean age of patients was 42±15 years. The mean duration of fever prior to hospitalization was 25±12 days and the mean time taken to reach a final diagnosis was 11±9 days. Infections, especially tuberculosis, were the most common cause of PUO, followed by connective tissue diseases and malignancies. PUO are due to rare presentation of common diseases and due to rare diseases.* ***Conclusion:*** *That's why the plan of first line investigation should be for Common diseases. There are several factors causing delay in diagnosis and it should be identified and overcome to improve outcomes.*

Keywords: *Pyrexia of Unknown Origin, Infections, Connective Tissue Diseases, Malignancy*

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1. *Associate Professor, Department of Medicine, Bangladesh Medical College, Dhaka, Bangladesh*
2. *Lecturere, Dhaka Dental College, Dhaka, Bangladesh*
3. *Associate Professor & Head, Department of Paediatrics, Bangladesh Medical College Hospital, Dhaka, Bangladesh*
4. *IMO, Bangladesh Medical College Hospital, Dhaka, Bangladesh*
5. *Registrar, Bangladesh Medical College Hospital, Dhaka, Bangladesh*

INTRODUCTION

Pyrexial diseases are common worldwide and affect all age groups and both sexes[1]. Most febrile conditions are readily diagnosed on the basis of presenting symptoms and a problem focused physical examination[2]. Simple testing such as complete blood count or urine examination, Ultrasonogram, X-Ray, Liver biochemestry are required to make a definitive diagnosis. Viral illness e.g. upper respiratory tract infections account for most of the self-limiting cases[3]. In few cases, the aetiology is not established even after a detailed history, thorough clinical ex- amination and routine investigations. Such prolonged febrile illnesses are usually present as pyrexia of unknown origin (PUO) or fever of unknown origin (FUO). The best definition of PUO was given by Petersdorf and Beeson in 1961 in a paper where they described 100 patients with PUO as a temperature of 38.3ºC (101ºF) or greater on several occasions, more than 3 weeks duration of illness and failure to reach a diagnosis despite 1 week of inpatient investigations[4]. While this definition has stood for 30 years, recently it has been revised and the definition proposed by Durack and Street is based on a new classification of PUO. PUO has been divided into four sub- types: classic, nosocomial, immune deficient (neutropenic), and HIV-associated[5]. The etiology includes infectious diseases, autoimmune conditions, neo- plastic disorders and some other rare conditions[6]. The etiology can be affected by the sociodemography of the sufferers[7]. The diagnostic workup for PUO is well described[8-14], but there is no gold standard for the work-up. The evolution of PUO begins by taking a thorough repeated history, repeated the physical examination, and with relevant laboratory tests, including biochemical tests, microbiological, immunological tests and radiological and imaging tests, biopsies and other invasive tests when required. Information obtained by taking history and physical examination, direct the physician to perform other relevant lab tests which can help provide an accurate diagnosis[15]. In Bangladesh, the majority of people are poor and live in rural areas and most of them have restricted health care. For that, the evaluation and diagnosis of even common illnesses to be difficult or delayed. Patients may not be diagnosed until they arrive at a tertiary health care center. Varying presentations of typical illnesses, deficiencies in the work-up on the part of the doctors, noncompliance on the part of the patients, not following-up or changing from doctor to doctor are reasons for a delay in diagnosis. Published information about PUO in Bangladesh is limited. The main objective of this study was to determine the etiology of PUO in our population to the understanding of the aetiology of PUO among patients presenting to a tertiary care center in Bangladesh.

METHODS & MATERIALS

A cross-sectional descriptive study was conducted at the Department of Medicine, Bangladesh Medical College Hospital, Dhaka, Bangladesh from January 2021 to December 2023. One hundred twenty-five patients with

prolonged fever fulfilling the PUO criteria of Petersdorf and Beeson with a history of a temperature >38.3oC on more than one occasion lasting longer than 3 weeks without a diagnosis after 3 days' evaluation in the hospital, three outpatient visits, or one week of logical and intensive outpatient workup without finding a cause and age > 18 years. were included in this study.

After taking informed consent, a detailed clinical history was obtained. All aspects of fever like its onset, character, duration, relieving and aggravating factors were recorded in detail on a specially designed proforma. A thorough review of systemic symptomatology was obtained. The respiratory and abdominal symptoms, musculoskeletal, skin was specially focused upon. After systemic review, all aspects of relevant past, family, travel, occupational, surgical and sexual histories were obtained in detail. Finally, a detailed history of current or past medications was also recorded in order to exclude the drug fever. The history was followed by meticulous clinical examination on admission and on daily basis. All except the most essential drugs were with- drawn. An accurate and hourly temperature chart in Fahrenheit was recorded by the trained and reliable staff nurses in their duty shifts supervised by assistant registrar. It helped us knowing the pattern of fever and also in excluding the possibility of factitious fever. The clinical findings were discussed with other consultants who helped in planning a diagnostic workup.

The initial workup included the routine laboratory tests like complete blood counts, Erythrocyte sedimentation rate, x-ray chest, urinalysis, liver function tests, urine and blood cultures and Ultrasonogram of abdomen. Some tests were repeated when found necessary. History and physical examination were repeated at each stage. The decisions to obtain further diagnostic studies were based on abnormalities found in the initial tests. imminological test like RA Anti CCP, ANA, P ANCA, C- ANCA, ENa profile, Imaging techniques like CT scans, MRI were carried out according to the continuous clinical assessment of the patients. smears for malarial parasites, ICT for Kala a zor More invasive procedures such as lumbar puncture, biopsy of bone marrow, liver, pleura, lymph nodes o.r aspiration of pleural, peritoneal or pericardial fluids were performed only when clinical suspicion showed that these tests were necessary.

All these and other relevant information were recorded in a objectively structured proforma. Statistical analysis was performed with SPSS version 25. Continuous variables, such as age, duration of fever before hospitalization, duration of hospitalization, time to reach diagnosis after hospitalization, were expressed as mean ±SD. Discrete variables, such as gender, diagnostic tests and diagnosis were expressed as percentages.

RESULTS

One hundred twenty-five (125) patients were included in the study; 64 (54.2%) were males,61 (48.8%) females. Age

ranged from 20 to 70 with mean age of the study group was 45±26 years. Among female patients, 40 (65.6%) were younger than 30 years while in males most 55(85.6%) were older than 45 years. Majority 65% of patients belonged to rural areas. A etiology could be ascertained in 83 (83%) while 17 (17%) remained undiagnosed despite repeated clinical assessment and extensive diagnostic workup. The mean duration of fever before hospitalization was 20±12 days, the meantime taken to reach a diagnosis (after hospitalization) was 12±9days and the mean duration of hospitalization was 18±9days **(Table I)**.

Table – I: Characteristics of Patients (*n*=125)

Variable	Patients (%) Mean±SD
Gender	
Male	64 (51.2)
Female	61 (48.8)
Age (mean±SD)	45±26
Duration of fever prior to hospitalization(mean±SD)	20±12
Duration of hospitalization (mean±SD	18± 9
Time to reach diagnosis(mean±SD)	12±9

A specific course of the fever was found in 105patients (84%). Infections were found to be the cause of fever in 60 patients 48%, while connective tissue diseases and malignancies, others were the cause of fever in 30, 20 and 15 patients 24%,16%and 12% respectively **(Table II)**.

Table – II: Casus of the Study Patients

Fever Course	*n*	%
Fever	105	84
No fever	20	16

In our study infection cases were 48% (60), connective tissue diseases 24 % (30), malifnancy 16% (20) and miscellaneous 12% (15) **(Table III)**.

Table III: Risk factor of the study patients

Risk factor	*n*	%
Infection	60	48
Connective tissue diseases	30	24
Malignancy	20	16
Miscellaneous	15	12

Culture results established the diagnosis in 22 patients (17.5%), biopsy revealed the diagnosis in 30 patients (24%), serology revealed the diagnosis in 28 patients (22.4%), imaging revealed the diagnosis in 30patients (24%) and multiple investigations and clinical course 5 patients (4%) **(Table IV)**.

Table – IV: Clinical Profile of the Study Patients

Diagnostic tests	*n*	%
Culture and sensitivity Blood	22	17.6
Bone marrow Urine Other body fluids	30	24

Biopsy Bone marrow Lymph node Liver Other organs and tissues	30	24
Radiology based diagnosis Serology based test	28	22.4
Clinical course relevant test-based diagnosis	05	4

Total tuberculosis (TB) 30, pulmonary TB (15 patients) were the most frequent infections. Of the extrapulmonary TB cases, abdominal TB (05 patients) was the most common followed by LN TB 5, tuberculous meningitis (2 patients), bone TB 2, and urogenital tuberculosis (1 patients) **(Table V)**.

Table – V: Frequent of Tuberculosis (TB)

Frequent Of Tuberculosis (TB)	*n*	%
Pulmonary TB	15	50
Abdominal TB	05	16.6
Lymph node TB	05	16.6
Brain TB	02	6.6
Bone TB	02	6.6
Urogenital TB	01	1.3

TB were the most common infective diseases followed by typhoid 15, and paratyphoid fevers 05 patients, liver abscess 4 patients, Lung abscess 2, others 4 patients were common infectious diseases **(Table VI).**

Table – VI: Table of Infection Causes Infections Presenting as Pyrexia of Unknown Origin

Infections Presenting	*n*	%
TB	30	24
Typhoid	15	12
Paratyphoid	05	4
Liver abscess	4	3.2
Lung abscess	2	1.6
Malaria	1	0.8
Kala a zar	1	0.8
Infective Endocarditis	1	0.8
Brucellosis	1	0.8

Of the connective tissue diseases, SLE11, Still's disease 06 was the most common followed by Vasculitis, polymyalgia rheumatica 05 patients and RA 03 patients **(Table VII)**.

Table – VII: Connective Tissue Diseases

Connective Tissue Diseases	*n*	%
SLE	11	36.6
Still Diseases	6	20
Vasculitis	5	16.6
Polymyalgia Rheumatica	5	16.6
Rheumatoid Arthritis	3	10

Of neoplasms 22 patients, Hodgkin's 05 patients, non-Hodgkin's lymphomas 04, CML 04 and HCC 5patients and carcinoma of the colon 02 patients were common **(Table VIII)**.

Table – VIII: Total Neoplasms of the Study Patients

Total Neoplasms	*n*	%
Hodgkin lymphoma	5	22.7
Non-Hodgkin lymphoma	4	18.1
CML	4	18.1
HCC	3	13.6
Colonic cancer	2	9.03

DISCUSSION

Comparisons of PUO patients between series are challenging because of the large number of causes of PUO and the impact of various factors on the relative proportions of causes. Geographic factors, referral patterns, length of studies and ages of patients have been shown to have an impact on the distribution of the various diagnostic categories[16]. In this study, infections (48.8%) were the most common cause of PUO, similar to other studies worldwide[12,13,17-22]. A large meta-analysis of 857 patients with PUO showed infections (47.0%) were the most common cause of PUO[23]. In a study of 98 Saudi patients[22] and 164 Romanian patients ***Baicus et al***, infectious diseases were found to be the cause of PUO in 32.7% and 45.1%, respectively[8]. Similar findings were reported by ***Handa et al.*** and ***Kejariwal et al.*** where infections comprised 53% and 43.8% of causes of PUO, respectively[18,24]. ***Moawad et al.*** and ***Hu et al.*** reported infections comprised lower percentages of PUO cases than other earlier studies ***Handa et al.***[21,22,24]. ***Abu Rahma et al.***,[6]; ***Kejariwal et al.***,[18]; ***Baicus et al.***,[8]; ***Colpan et al.***,[12] but were still the most common cause of PUO. Infectious etiologies of PUO vary by location. ***Handa et al.***,[24] and ***Jung et al.***[25] found infective endocarditis and enteric fever were the most common infectious causes of PUO, while our study found various forms of tuberculosis as the most common infections among patients with PUO. The percentage of infectious diseases in our study was 57% which is comparable to the results of other studies like in ***Saltoglu et al.*** (58%),[26] ***Zamir et al.*** (54.5)[27] and in ***Kejariwal et al***. (53%)[18]. Among infections, tuberculosis was the most common cause (32%). This percentage is much higher than the results of ***Saltoglun's*** study (17.2%)[26]. This is not unexpected as the disease is prevalent in Khyber Pakhtun Khwa province where more than 3 million Afghan refugees are residing in environmental conditions favourable to the transmission of tuberculosis. Fifty percent of the patients suffering from TB were Afghan refugees residing in the different villages of Peshawar. Majority of patients with PUO due to TB were females, i.e. 65%. This high percentage can be attributed to the gen- der discrimination in our society where due medical care to the female family members is not pro- vided. So, the diagnosis and proper treatment of female patients is often delayed. The prevalence of TB in younger age group i.e. less than 40 years in our study was noted. It shows the failure of TB control program and inadequate BCG vaccination. Other studies have also found tuberculosis as the most common infection among PUO patients[12,18,22,24,28]. Abdominal TB was the most common extrapulmonary form

of TB found in our study followed by tuberculous meningitis, urogenital TB, TB lymphadenitis, TB arthritis and Pott's disease. Extra-pulmonary TB causes diagnostic problems. CT scans, MRI scans and rapid diagnostic tests on body fluids may be required to make the diagnosis. The percentage of malaria in our study was found to be 6% reported it to be 12.8%. The striking difference is due to the fact that clinical malarial cases (e.g. without confirmatory laboratory evidence but positive therapeutic response) were excluded from our study but included in the above-mentioned study. Plasmodium falciparum caused a significant number of PUOs i.e. 50%. It is due to the fact that plasmodium falciparum is rarely seen in the venous blood which is commonly taken for making blood smears. It lives in the capillaries of reticuloendothelial system. This is why capillary blood taken by finger prick or bone marrow smears diagnosed plasmodium falciparum malaria in our patients. Secondly chloroquine taken already by many patients before hospital admission could not cure their fever. It is chiefly because that plasmodium falciparum malaria is mostly resistant to chloro- quine and partly because the dosage taken were improper. Abdominal abscesses, typhoid fever and falciparum malaria were frequent infectious causes of PUO in our study, but other studies ***Hu et al.*** and ***Moawad et al.***[21,22] did not find these causes very frequently. The frequency of these dis- eases in our study may be explained by an unhealthy environment, contaminated drinking water, unhealthy food handlers and a paucity of health facilities. Connective tissue diseases and neo- plasms were other causes of PUO in this study at 12.7% each. Our findings are similar to those of ***Moawad et al.,***[22] who found connective tissue disease comprised 14% of FUO cases. ***Tabak et al.***[20] and ***Kucukardali et al.***[29] found connective tissue disease comprised 23% and 30.5% of PUO cases, respectively. In our study, adult Still's disease was the most common connective tissue disease found in younger patients and polymyalgia rheumatica was the most common in older patients, similar to other studies[17,21,22]. Adult Still's disease has been recognized as an important cause of PUO[19,29]. A retrospective study ***Abid*** and ***Khalid, et al.***[5] from Pakistan found only 13 patients with Still's disease in a 10-year period. In another multicenter prospective study at a tertiary care hospital, Still's disease was the most common non-infectious inflammatory disease causing PUO (13.6%)[19]. Hodgkin's lymphoma and non-Hodgkin's lymphoma were the most common neoplasms causing PUO in our study, similar to other studies[18,21,22]. CT and MRI imaging have markedly improved the detection of tumors. However, the diagnosis of hematological malignancies can still be difficult because of the absence of localizing features and the diverse nature of these diseases. The mean duration of fever in this study prior to hospitalization was 37±16 days and the mean time taken to reach a diagnosis (after hospitalization) was 19±14 days. Some studies from the West De Kleijn *et al*; Vanderschueren *et al*.[13,30] found the duration of hospitalization to range

between 17 and 27 days. Approximately 11.7% of cases in our study remained undiagnosed, similar to other studies[17,18,21,22]. The mortality rate and number of undiagnosed cases of PUO in our study were higher than in the above mentioned studies. The outcomes of PUO depend on the cause, complications and time to reach the diagnosis. Sixty percent of the rural population of Pakistan has inadequate access to quality health care, which is a main factor in the delay in diagnosis and outcomes. In our study 12% of PUO cases were due to collagen vascular diseases. This finding is comparable to the studies from India by ***Kejariwal D et al.***[18] (11%) and from Northern Pakistan by ***Iftikhar et al.*** (13%)[31]. Among 12 patients with PUO due to collagen vascular diseases 10 were females. It is because of high prevalence of collagen vascular diseases among females. The neoplastic diseases comprised 10% of the disease spectrum in our study. The percent- age of neoplastic diseases presenting as PUO is different in different studies. A recent study by ***Zamir et al.***[27] reported this percentage to be 7.9% while ***Ifrikhar et al.***[31] found that 19% of PUO cases were due to neoplastic diseases. The importance of imaging in the work-up of PUO cannot be over emphasized. Rural health care systems should be equipped with conventional radiology and ultrasonography facilities and tertiarycare hospitals should be equipped with a spiral CT and an MRI[32]. In Pakistan many public and private tertiary care hospitals do not have an MRI, leukocyte scans or important rheumatologic investigations, such as p-ANCA, c-ANCA and glycosylated ferritin. The diagnostic delay in PUO patients has multifactorial etiologies at all levels: the disease level, patient level, referring physician level and health care facility level. The causes of PUO and their relative frequencies in a population should be known because PUO is usually caused by either an unusual presentation of a common disease or an uncommon condition. Frequent diseases, rather than rare ones, should be considered first when investigating PUO cases. Factors responsible for delay should be identified and overcome to improve the prognosis. ***Similarly Saltoglu et al.*** reported 13.9% of prolong fevers due to malignant diseases[26]. However the number of neo- plastic diseases presenting as PUO has decreased to less than 20%. It may be due to the availability Aetiology of pyrexia of origin in tertiary care hospital We have been successful in diagnosing 83% of cases but 17% remained undiagnosed. This finding can be compared to the study results of ***Khan et al.***[33] from Mayo Hospital Lahore (22%). The un-diagnosed cases were advised regular checkup every fortnightly or to report if any new symptom or sign developed. Only 10 patients co-operated in follow up. All of them spontaneously improved except one patient who died 5 months later. Some of the undiagnosed patients did not come for follow up.

Conclusions

Pyrexia of unknown origin is predominantly caused by infections, lead by tuberculosis followed by typhoid fever, malaria and infective endocarditis.

Collagen vascular diseases and neoplasms are next to infections. A significant number of PUO remains undiagnosed.

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Conflict of Interest

The authors declare no conflict of interest.

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