

STUDY OF SPECTRUM OF PYREXIA OF UNKNOWN ORIGIN PATIENTS IN A TERTIARY CARE HOSPITAL IN COASTAL ANDHRA PRADESH

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ABSTRACT

BACKGROUND

Pyrexia of Unknown Origin (PUO)/Fever of Unknown Origin (FUO) was defined in 1961 by Petersdorf RG and Beeson PB² as the following- A temperature greater than 38.3°C (101°F) on several occasions; more than 3 weeks' duration of illness; and failure to reach a diagnosis despite 1 week of inpatient investigation.

The aim of the study is to study the spectrum of cases of Pyrexia of Unknown Origin (PUO)/Fever of Unknown Origin (FUO) in a tertiary care hospital in coastal Andhra Pradesh.

MATERIALS AND METHODS

All patients with PUO admitted under the Department of General Medicine in the NRI Institute of Medical Sciences (Anil Neerukonda Hospital) Sangivalasa, Visakhapatnam, during the period from 1st September, 2016, to 31st August, 2017, and who fulfil inclusion and exclusion criteria of classic PUO defined by Durrack and AC street¹ were selected for the study.

RESULTS

The present study included 34 patients with pyrexia of unknown origin in which the patients' age ranged from 15 years to 77 years. Most of the cases, 41.2% were in the age group 21 to 40 years and 35.3% in the age group 41 to 60 yrs. This indicates PUO is common in middle age group in our study.

CONCLUSION

Noninfectious causes like collagen vascular disease and neoplasms are becoming important differential diagnosis. But, in India, infections like tuberculosis, enteric fever are still the most common cause of FUO.

KEYWORDS

Pyrexia of Unknown Origin, Fever of Unknown Origin, Spectrum.

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BACKGROUND

Pyrexia of Unknown Origin (PUO)/Fever of Unknown Origin (FUO) was defined in 1961 by Petersdorf RG and Beeson PB² as the following-

- a. A temperature greater than 38.3°C (101°F) on several occasions.
- b. More than 3 weeks' duration of illness.
- c. Failure to reach a diagnosis despite 1 week of inpatient investigation.^{3,4}

In 1991, DT Durrack and AC Street¹ suggested few changes to the earlier definition and proposed four following types of FUO.¹

Current Types of Fever of Unknown Origin¹ (PUO)

Classic FUO- When temperature is more than or equal to 38.3°C (101°F) recorded on several occasions occurring more than 3 weeks undiagnosed in spite of investigations on 3 OPD visits or 3 days of stay in hospital or 1 week of invasive ambulatory investigations is called classic FUO.¹

Nosocomial FUO- When temperature more than 38.3°C (101°F) is recorded on several occasions in a hospitalised patient who is receiving acute care and in whom infection was not manifested or incubating on admission is called nosocomial FUO. Three days of investigations including at least 2 days incubation of cultures is the minimum requirement for this diagnosis.¹

Neutropenic FUO (Immune Deficient FUO)- This is defined as a temperature of more than or equal to 38.3°C

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(101°F) on several occasions in a patient whose neutrophil count is less than 500/ μ L or is expected to fall to that level in 1-2 days and a specific cause is not identified after 3 days of investigations including at least 2 days of incubation of cultures.¹

Human Immunodeficiency Virus Associated FUO- This is defined as temperature more than or equal to 38.3°C or ($\geq 101^{\circ}\text{F}$) on several occasions over a period of 4 weeks for outpatients or more than 3 days for hospitalised patients with HIV infection when appropriate investigations for 3 days including 2 days incubation of cultures reveal no source.¹

There are well over 200 different reported causes of FUO.^{6,7,8} To date, there are no published guidelines or evidence-based recommendations for the diagnostic workup of FUO.

Outcomes of patients with FUO is a function of the underlying cause.^{9,10,11,12,13} Overall, 12% to 35% of patients will die from FUO-related causes; 52% to 100% of patients with a final diagnosis of malignancy will die within 5 years of the diagnosis.^{9,10,11,12,13} Mortality is much lower if an infection is identified as the cause of FUO (8%-22%). Therefore, the best predictor of survival is disease category with malignancy incurring the highest mortality. The prognosis of patients with FUO in whom a cause cannot be identified is excellent. Most of these patients have a spontaneous recovery (51%-100%) and only a small proportion have persistent fever (0%-30%).

Objectives

$$\text{Sample size} = \frac{Z_{1-\alpha/2}^2 p(1-p)}{d^2}$$

Here

$Z_{1-\alpha/2}$ = Is standard normal variate (at 5% type 1 error ($P < 0.05$) it is 1.96 and at 1% type 1 error ($P < 0.01$) it is 2.58). As in majority of studies P values are considered significant below 0.05 hence 1.96 is used in formula.

p = Expected proportion in population based on previous studies or pilot studies.

d = Absolute error or precision – Has to be decided by researcher.

- To investigate the cause of PUO in admitted patients.
- To find the relative incidence of different causes.
- To formulate a cost-effective working formula for approach to a case of PUO in our setting.

Common Aetiologies of Fever of Unknown Origin in India¹⁴

Infections¹⁴

Tuberculosis especially extrapulmonary, abdominal abscess, pelvic abscess, dental abscesses, endocarditis, osteomyelitis, sinusitis, prostatitis, viral (cytomegalovirus,

Epstein-Barr, HIV) rickettsial, fungal, malaria, typhoid and kala azar.

Malignancies⁶

Lymphoma, chronic leukaemia, metastatic cancer, renal cell carcinoma, colon cancer, hepatoma and sarcomas.

Autoimmune Conditions⁶

Adult Still's disease, polymyalgia rheumatica, temporal arteritis, SLE, RA, Reiter's syndrome, vasculitis and inflammatory bowel disease.

Miscellaneous⁶

Drug-induced fever, factitious fever, sarcoidosis, granulomatous hepatitis, DVT and PTE.

MATERIALS AND METHODS

This study was undertaken at the NRI Institute of Medical Sciences (Anil Neerukonda Hospital), a tertiary care hospital in the coastal Andhra Pradesh, Sangivalasa, Visakhapatnam of Andhra Pradesh State of India for a period of one year from 1st September 2016 to 31st August 2017.

Selection of Patients- All patients with PUO admitted under the Department of General Medicine in the NRI Institute of Medical Sciences (Anil Neerukonda Hospital) Sangivalasa, Visakhapatnam, during the period from 1st September 2016 to 31st August 2017 and who fulfil inclusion and exclusion criteria of classic PUO defined by Durrack and AC Street were selected for the study. After informed consent, patients were included in the PUO protocol, which consists of a standardised pre-coded history, thorough physical examination and relevant necessary investigations. Clearance was obtained from the ethical committee of the hospital for the study.

Sample Size- Sample size was estimated by using the proportion of PUO in tertiary care hospital from the pilot study in our institute as 2%. At 5% absolute error and 95% confidence level sample size was estimated by using the below formula.

$P = 2$ or 0.02 .

$q = 98$ or 0.98 .

$d = 5\%$ or 0.05 .

Using the above values at 95% confidence level, a sample size of 31 subjects with PUO will be included in the study.

Considering 10% nonresponse, a sample size of $31 + 3 = 34$ subjects will be included in the study.

34 patients who fulfilled the inclusion and exclusion criteria were selected for this study.

Inclusion Criteria

1. Oral temperature of $>38.3^{\circ}\text{C}$ ($>101^{\circ}\text{F}$) on several occasions.
2. Duration of fever of >3 weeks.

3. Failure to reach a diagnosis in spite of investigations on 3 OPD visits or 3 days of stay in hospital or 1 week of invasive ambulatory investigations.

Exclusion Criteria

1. Patients on steroids.
2. Patients with known malignancy.
3. Patients known to have HIV infection.
4. Age less than 14 years.
5. Patients having undergone any invasive procedure or surgery in the last 3 months.
6. Patients taking antitubercular drug or having taken it in the last 3 years.

Collection of Sample

Detailed history with regard to the presenting complaint was taken that included demographic profile. History was obtained from the patients by direct questioning or in case of patients with altered sensorium from close relatives. A detailed clinical evaluation was done as per the proforma.

Investigations were ordered depending upon the history and clinical examination to look for a possible cause of prolonged fever.

First line of investigations were complete haemogram with peripheral smear examination including examination for malarial parasite, urine analysis, blood, sputum and urine culture and sensitivity studies, Widal, Typhidot IgM, ANA, chest x-ray, USG abdomen and body fluid analysis (CSF, ascitic fluid, pleural fluid). CBC was done using 5 part differential method with Sysmex XT-1800i machine. Serum creatinine was done using Jaffe method with VITROS 350 machine. Urine, sputum and body fluids (CSF, ascitic fluid, pleural fluid) analysis and culture sensitivity studies were done using Wesco microscopy.

Sputum or body fluids (CSF, ascitic fluid, pleural fluid), AFB examination was done using Ziehl-Nelsen method with Wesco microscopy.

Widal test was done using standard tube method and Typhidot IgM assay was done using Typhidot rapid IgG/IgM (combo) kit. Weil-Felix test was done using standard tube method.

ANA was tested using indirect Immunofluorescence Antinuclear Antibody Test (IF-ANA) method. HIV was done by ELISA method and if positive confirmed by Western blot. LFT, lipid profile and serum electrolytes were done.

ABG, chest x-ray, CT scan, ultrasonography and echocardiography was done.

Method of Statistical Analysis

Data was entered into Microsoft excel datasheet and was analysed using SPSS 22 version software and EPI info CDC Software. Categorical data was represented in the form of frequencies and proportions. Continuous data was represented as mean and standard deviation. Bar diagrams and Pie charts were plotted to represent the data graphically. Open Epi software was used to calculate the sample size 'p' value <0.05 was considered as statistically significant.

RESULTS

In the study, a total of 34 subjects with PUO were included in the study and were analysed to find the demographic profile and clinical profile.

		Frequency	Percent
Age	<20 years	3	8.8
	21 to 40 years	14	41.2
	41 to 60 years	12	35.3
	>60 years	5	14.7
	Total	34	100

Table 1. Age Distribution of Subjects

Mean age of subjects in the study was 40.53 ± 16.47 years. Majority of subjects were in the age group 21 to 40 years (41.2%) and 35.3% in the age group 41 to 60 yrs. This indicates PUO was common in middle age group in our study.

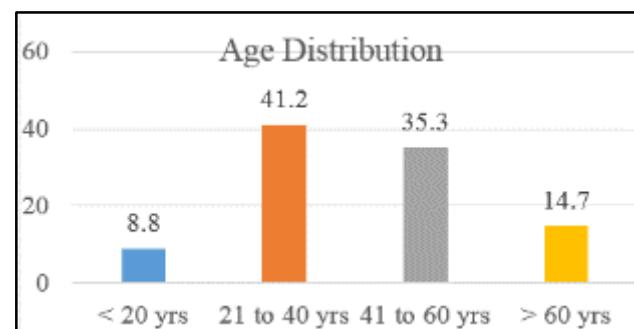


Figure 1. Bar diagram Showing Age Distribution of Subjects in the Study

		Frequency	Percent
Gender	Female	12	35.3
	Male	22	64.7
	Total	34	100

Table 2. Gender Distribution of Subjects

In the study, 64.7% were males and 35.3% were female. PUO is more common in males than females in the current study.

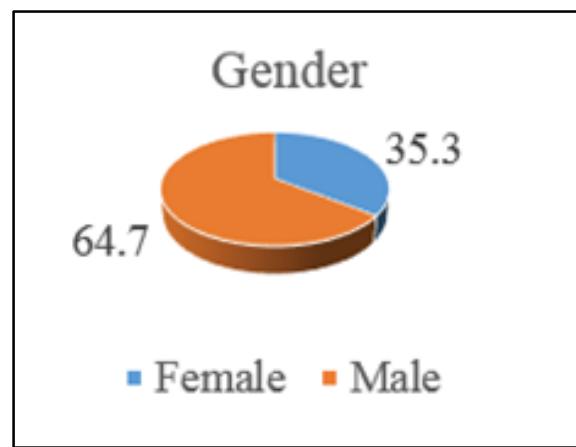
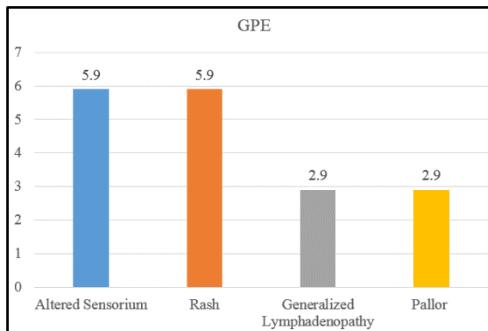


Figure 2. Pie Diagram Showing Gender Distribution of Subjects

	Frequency	Percent
General physical exam	Altered sensorium	2
	Rash	2
	Generalised lymphadenopathy	1
	Pallor	1

Table 3. Physical Examination Findings in the Study

On general physical examination, 2 subjects had altered sensorium and rash respectively and 1 subject had generalised lymphadenopathy and pallor, respectively.

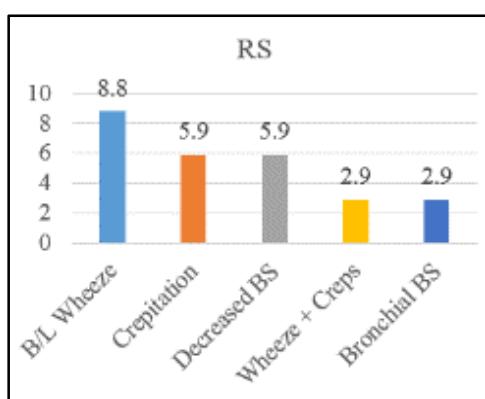
**Figure 3. Bar Diagram showing Physical Examination Findings in the Study**

On general physical examination, 28 patients (82.4%) had no significant positive findings on general physical in the current study, out of 34 patients with PPUO only 6 patients (17.6%) had significant findings examination.

	Frequency	Percent
Respiratory System	No abnormal findings	25
	Bilateral wheeze	3
	Crepitations	2
	Decreased breath sounds	2
	Wheeze + crepitations	1
	Bronchial breath sounds	1
	Total	34

Table 4. Respiratory System Findings

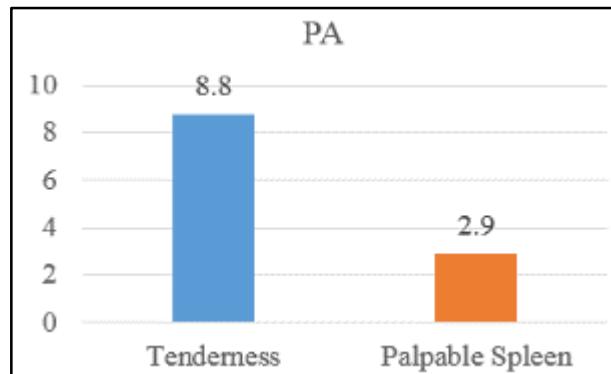
In the study, most of the patients, 25 (73.5%) had no significant findings on respiratory system examination. 9 subjects had significant positive respiratory findings. Of them, 3 subjects had bilateral wheeze, 2 subjects had crepitation and decreased breath sounds respectively and 1 subject had bronchial breath sounds and wheeze + crepitations, respectively.

**Figure 4. Bar Diagram Showing Respiratory System Findings in the Study**

	Frequency	Percent
Abdomen Examination	No abnormal findings	30
	Tenderness	3
	Palpable spleen	1
	Total	34

Table 5. Per Abdomen Findings in the study

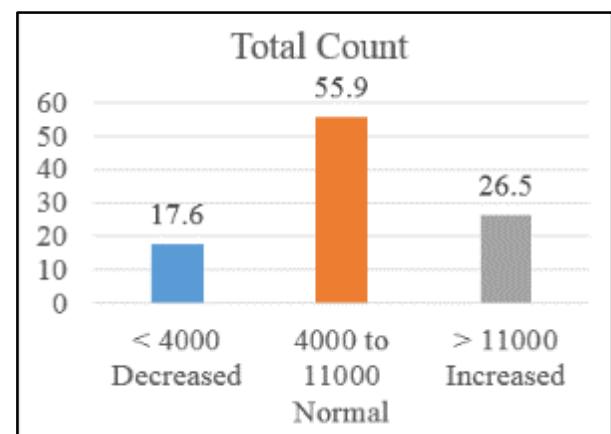
In the study, most of the patients, 30 (88.2%) had no significant positive findings on per abdomen examination. Only 3 subjects had per abdomen tenderness and 1 subject had palpable spleen on examination.

**Figure 5. Bar Diagram showing per Abdomen Findings in the Study**

	Frequency	Percent
Total count	<4,000 decreased	6
	4,000 to 11,000 normal	19
	>11,000 increased	9
	Total	34

Table 6. Total Count in Subjects with PPUO

Out of 34 subjects, 17.6% had leucopenia and 26.5% had leucocytosis. In all others, total count was in normal range. In the study, 2 subjects had thrombocytopenia.

**Figure 6. Bar Diagram Showing Total Count in Subjects with PPUO**

	Frequency	Percent
Urine routine	Normal	28
	Albuminuria	4
	Pus cells	2
	Total	34

Table 7. Urine Routine Findings in Subjects

Out of 34 subjects, only 4 subjects had albuminuria and 2 had pus cells. Urine analysis is normal in rest of the patients, 28 (82.4%).

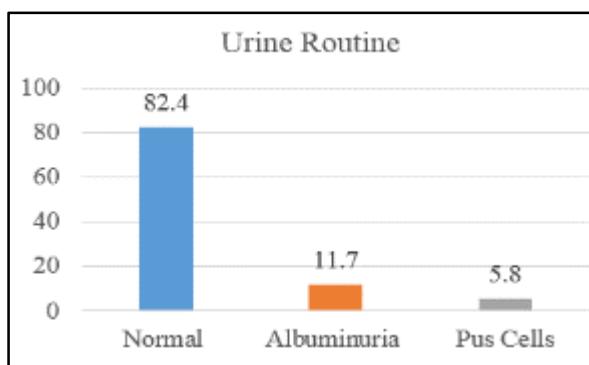


Figure 7. Bar Diagram Showing Urine Routine Findings in Subjects

		Frequency	Percent
Culture Findings	Blood C/S - S. Typhi	1	2.9
	Sputum - Candida	1	2.9
	Urine C/S - E. coli and M. tuberculosis	1	2.9
	Urine C/S - E. coli	1	2.9

Table 8. Culture Findings in the Study

Only 4 subjects in the study showed positive culture. In 1 subject, blood culture was positive for *S. typhi*; in 1 subject, sputum culture was positive for *Candida*; in one subject, urine culture for *E. coli* and *M. tuberculosis* and *E. coli* alone, respectively.

In the current study of 34 patients, culture (blood, urine or sputum) did not show any significant growth in most of the patients, 30 (88.2%).

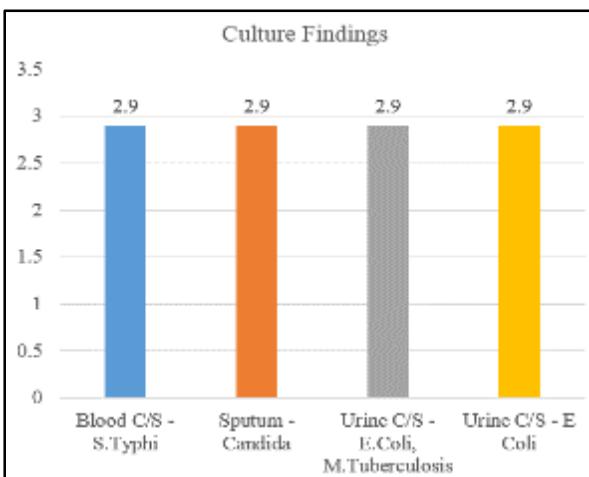


Figure 8. Bar Diagram showing Culture Findings in the Study

	Positive		Negative	
	Frequency	Percent	Frequency	Percent
MP smear	1	2.9	33	97.1
Widal test	4	11.8	30	88.2
Typhidot IgM	4	11.8	30	88.2
Weil-Felix	4	11.8	30	88.2
ANA	1	2.9	33	97.1

Table 9. Results of Various Other Investigations

In the study, one subject was positive in MP smear for *P. vivax* and ANA positive respectively and 4 subjects were positive for Widal test, Typhidot IgM and Weil-Felix test, respectively.

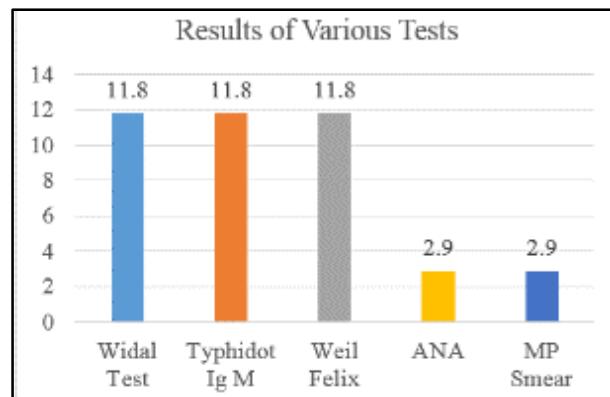


Figure 9. Bar Diagram showing Results of Various Investigations

			Frequency	Percent
	Normal		29	85.3
Chest x-ray findings	Pleural effusion	Bilateral	1	2.9
		Right side	1	2.9
	Pneumonia	Left basal	1	2.9
		Left lower zone	1	2.9
	Cavity	Right upper zone	1	2.9
		Total	34	100

Table 10. Chest X-Ray Findings in Subjects

In the current study of 34 patients of PUO, 29 patients (85.3%) had normal chest x-rays. Only 5 patients (14.7%) had positive findings on chest x-ray.

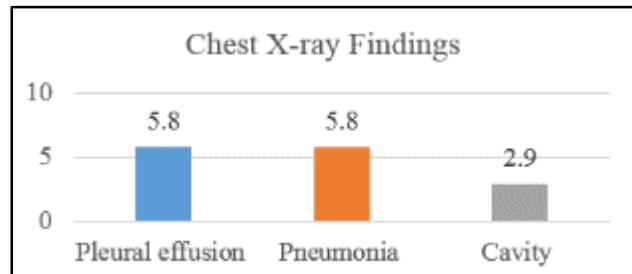


Figure 10. Bar Diagram Showing Chest X-Ray Findings in Subjects

			Frequency	Percent
	Normal		21	61.8
USG abdomen findings	Hepatosplenomegaly	6	17.6	
	Splenomegaly	3	8.8	
	Hepatomegaly	2	5.9	
	Hepatosplenomegaly, ascites	1	2.9	
	Para-aortic lymph nodes enlarged	1	2.9	
	Total	34	100	

Table 11. USG Abdomen Findings in Subjects

In the current study of 34 patients of PUO, 21 patients (61.8%) had no positive findings on USG abdomen. 13 patients (38.2%) had positive findings on USG abdomen.

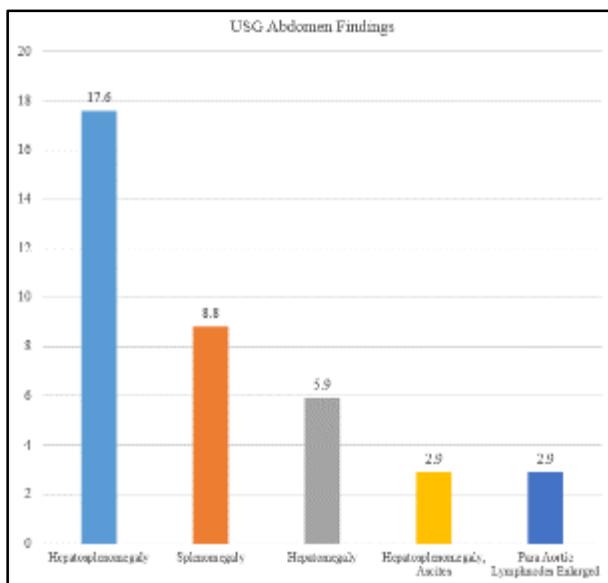


Figure 11. Bar Diagram Showing USG Abdomen Findings in Subjects

	Frequency	Percent
Body fluid analysis	CSF - TB meningitis	1
	Pleural fluid - ADA high	1
	Sputum AFB - positive	1

Table 12. Body Fluid Analysis in Subjects

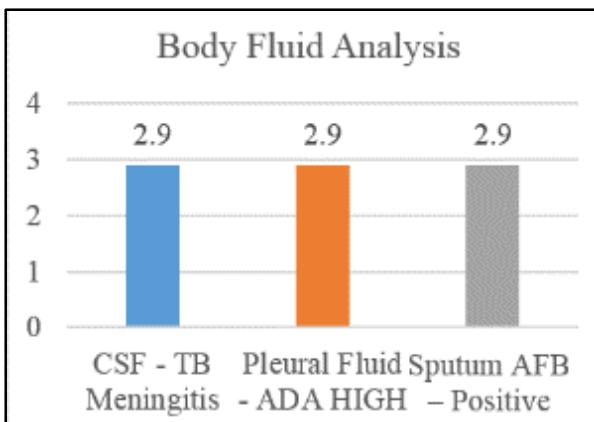


Figure 12. Bar Diagram Showing Body Fluid Analysis Results in Subjects

In this study of 34 patients, body fluid analysis was done in 4 patients. CSF analysis in 2 patients, of which one patient's analysis was normal and other patient's analysis was suggestive of TB meningitis. Pleural fluid analysis was done in one patient, which showed high ADA levels suggestive of pleuropulmonary TB. Sputum analysis in one patient was positive for AFB suggestive of pulmonary TB.

	Frequency	Percent
Special Tests	HIV Elisa +ve	3
	Brucella IgM +ve	1
	Brucella IgM +, 2D echo - hypokinesia	1
	2D echo - Mild pericardial effusion, S. ferritin -High	1

CECT thorax - cavity with surrounding consolidation right side	1	2.9
CT/MRI brain - granulomas with obstructed hydrocephalus	1	2.9
Dengue serology - IgG +	1	2.9

Table 13. Special Tests Results in Subjects

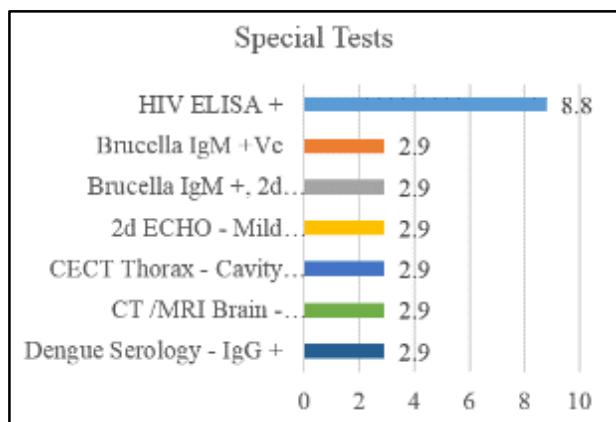


Figure 13. Bar Diagram showing Special Tests Results in Subjects

Diagnosis	Frequency	Percent
Undiagnosed	11	32.4
TB	Pulmonary TB	1
	Pleuropulmonary TB	1
	TB meningitis	1
	Genitourinary TB	1
	Enteric fever	5
Infectious	Rickettsial fever	4
	HIV infection	3
	Brucellosis	2
	Dengue fever	1
	Malaria	1
	Pneumonia	1
	UTI	1
Non-Infectious	Still's disease	1
Total	34	100

Table 14. Diagnosis of Subjects in the Study

In the study of 34 patients of PUO, 11 patients (32.4%) were undiagnosed and in other 23 patients (67.6%) diagnosis could be made.

Out of these 23 patients, 22 patients (64.7% of PUO) had infectious and only 1 patient (2.9% of PUO) had non-infectious causes for PUO.

Among the infectious causes, 4 patients (11.6% of PUO) had tuberculosis and 18 patients (53.1% of PUO) had other than TB causes.

Among non-TB causes, 5 subjects (14.7% of PUO) had enteric fever, 4 subjects (11.8% of PUO) had rickettsial fever, 3 subjects (8.8% of PUO) had HIV, 2 subjects (5.9% of PUO) had brucellosis and 1 subject had dengue, malaria and UTI (2.9% each), respectively.

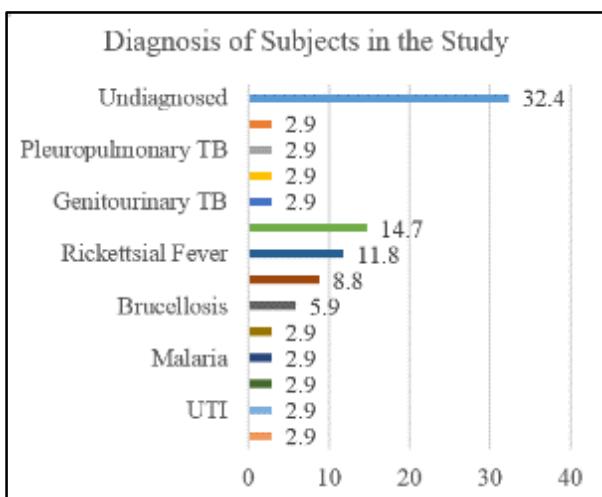


Figure 14. Bar Diagram Showing Diagnosis of Subjects in the Study

DISCUSSION

Comparison between series of patients with PUO is difficult because of the large number of possible causes and the influence of numerous factors on the relative proportion of the various diagnostic categories.

In our study, we enrolled 34 patients of PUO who were admitted in our hospital from 1st September 2016 to 31st August 2017 after satisfying the inclusion/exclusion criteria.

Age and Sex- The present study included 34 patients of PUO in which the patient's age ranged from 15 years to 77 years. Mean age of subjects in the study was 40.53 ± 16.47 years. Majority of subjects were in the age group 21 to 40 years (41.2%) and 35.3% in the age group 41 to 60 yrs. This indicates PUO was common in middle age group in our study.

This is similar to the studies by Dipanjan Bandyopadhyay⁵ et al where mean age in PUO is 42.33 ± 14.85 years and D Kejariwal¹⁵ et al where mean age is 32.4 years (range 12-65 years).

In the current study, 64.7% of the patients are males and 35.3% are females. In contrast to the studies by D Kejariwal¹⁵ et al where 59% were males and 41% were females and Dipanjan Bandyopadhyay⁵ et al where 50% were males and 50% were females. This indicates that PUO is more common in males than females in the current study.

Physical Examination Findings- In the current study, out of 34 patients with PUO, only 6 patients (17.6%) had significant findings on general physical examination. 28 patients (82.4%) had no significant positive findings on general physical examination.

In the study, most of the patients, 25 (73.5%) had no significant findings on respiratory system examination, only 9 subjects had significant positive respiratory findings.

In the study, most of the patients, 30 (88.2%) had no significant positive findings on per abdomen examination. Only 3 subjects had per abdomen tenderness and 1 subject had palpable spleen on examination.

None of the patients had significant positive findings on neurological or cardiovascular examination.

Investigations- In our study, preliminary investigations like haemogram with peripheral smear, urine analysis, blood and urine C/S studies, chest x-ray and USG abdomen were normal in most of the patients.

Out of 34 subjects, haemogram was normal in most of the patients. 17.6% had leucopenia and 26.5% had leucocytosis. In all others, total count was in normal range. In the study, only 2 subjects had thrombocytopenia.

Out of 34 subjects, urine analysis is normal in 28 (82.4%) of the patients, only 4 subjects had albuminuria and 2 had pus cells.

In the culture sensitivity studies, culture (blood, urine or sputum) did not show any significant growth in most of the patients, 30 (88.2%).

Only 4 subjects in the study showed positive culture. In 1 subject, blood culture was positive for *S. typhi*; in one subject, sputum culture was positive for candida; in one subject, urine culture for in *E. coli* and *M. tuberculosis* and *E. coli* alone, respectively.

In the current study, smear for malarial parasite, Weil-Felix, Widal, Typhidot IgM and ANA were done for all the 34 patients. But, only one subject was positive in MP smear for *P. vivax* and ANA positive respectively and 4 subjects were positive for Widal test, Typhidot IgM and Weil-Felix test, respectively.

Imaging- Chest x-ray and USG abdomen were done in all the 34 patients in the current study.

Out of the 34, 29 patients (85.3%) had normal chest x-rays. Only 5 patients (14.7%) had positive findings on chest x-ray and 21 patients (61.8%) had no positive findings on USG abdomen. 13 patients (38.2%) had positive findings on USG abdomen.

CT and MRI Studies- CT and MRI studies were done in 5 of the 34 patients in the current study. Of which, these studies helped with the diagnosis in only 2 patients.

CT thorax suggestive pulmonary TB in one patient and CT brain suggestive of tubercular granulomas of the brain in one patient.

Nuclear Imaging- FDG PET - CT scan was done in one of the 34 patients in our study. Though the scan did not reveal any diagnostic clue in this case, it is done as a part of the diagnostic workup to establish an early diagnosis.

Spectrum of PUO- Aetiological Profile

PUO of Indeterminate Cause

In the current study of 34 patients of PUO, diagnosis could be made in 23 patients (67.6%) and the other 11 patients (32.4%) were undiagnosed.

The incidence of PUO of indeterminate cause, i.e. undiagnosed cases ranged from 4.7% to 19% in previous studies, while in our study, it is 32.4%.

This is similar to the study of 167 patients with De Kleijn EM, Vandenbroucke JP, van der Meer JW et al¹⁶ of the Netherlands PUO study group where diagnosis could not be made in 29.9% of the patients.

In the pilot study of 100 patients of PUO by Petersdorf, Beeson et al,² diagnosis could not be made in 7% of the patients.

In the study of 100 patients by Kejariwal et al,¹⁵ 14% of the cases remained undiagnosed and 12% of cases were undiagnosed in a study of 164 cases by Dipanjan Bandyopadhyay et al.⁵

	Current Study	Petersdorf et al	Kejariwal et al	Bandyopadhyay et al
Total Cases	34	100	100	164
Undiagnosed	32.4%	7%	14%	12%
Diagnosed	67.6%	93%	86%	88%

Table 15

Infections	64.7%	36%	53%	55%
Collagen Vascular Diseases	2.9%	13%	11%	11%
Malignancies	-	19%	17%	22%

Table 16

This study, in contrast to the study by De Kleijn EM, Vandenbroucke JP, van der Meer JW et al¹⁶ of the Netherlands PUO study group, which showed the changing spectrum of diseases causing PUO and increasing trend of noninfectious causes in the western world shows that infectious diseases remain the leading cause in the developing country like India.

In contrast to the previous Indian studies by Kejariwal et al and Dipanjan Bandyopadhyay et al, where tuberculosis was the most common infectious cause, enteric fever is the most common cause in the current study with tuberculosis and rickettsial fevers as the second most common causes.

In the current study, out of the 34 patients, 5 subjects (14.7% of PUO) had enteric fever, 4 subjects (11.8% of PUO) had rickettsial fever and tuberculosis, respectively, 3 subjects (8.8% of PUO) had HIV, 2 subjects (5.9% of PUO) had brucellosis and 1 subject had dengue, malaria and UTI (2.9% each), respectively.

Non-Infectious Causes

Collagen vascular disorders- In our study, only 1 patient was diagnosed with noninfectious cause. Out of the 34 patients, only one patient had autoimmune aetiology and diagnosed with Still's disease.

This is in contrast to other Indian studies by Kejariwal et al and Dipanjan Bandyopadhyay et al where 11% of the patients in each study were diagnosed autoimmune conditions.

Neoplasms- In the current study, none of the patients had neoplasms in contrast to the studies by Kejariwal et al and Dipanjan Bandyopadhyay et al where 17% and 22% of the patients had neoplasms as the aetiology for PUO, respectively.

Infectious Causes- In the current study, infectious diseases were found to be the leading cause of the PUO. 22 of the 34 (64.7%) patients in the study were diagnosed with the infectious diseases.

This is higher when compared to the pilot study of 100 patients by Petersdorf, Beeson et al, where 36% of the cases had infectious causes and also higher when compared to other Indian studies by Kejariwal et al and Dipanjan Bandyopadhyay et al where the infectious causes were 53% and 55%, respectively.

Global Spectrum of FUO⁶

The spectrum of FUO aetiology may include more than 200 diseases. According to studies conducted to date, the diseases taking part in FUO aetiology and their rates are as follows- infections (21-54%), noninfectious inflammatory causes (13-24%), neoplasms (6-31%) and other causes (4-6.5%).

Spectrum of PUO in India- D Kejariwal, N Sarkar, SK Chakraborti, V Agarwal, S Roy et al of Department of Medicine, Institute of Postgraduate Medical Education and Research and SSKM Hospitals, Calcutta, India, did a prospective study of 100 cases of PUO admitted in the Department of General Medicine in their tertiary referral Centre during a 3-year period from May 1998 to April 2001.¹⁵ It showed that infections especially tuberculosis remains the most important cause of PUO in India despite the decreasing importance of infections as cause of PUO in the western literature.¹⁵

More recently, in 2011, an aetiological study of PUO in patients admitted to medicine ward of a teaching hospital of eastern India was done in which Bandyopadhyay D, Bandyopadhyay R, Paul R, Roy D et al showed that the main diagnosis in the end was tuberculosis closely followed by haematological malignancy. A substantial number of cases remained undiagnosed despite all investigations. The provisional diagnosis matched with the final in and around two thirds of the cases. While for younger patients, leukaemia was a significant diagnosis for older ones, extrapulmonary tuberculosis was a main concern.

They concluded that in India, infectious disease still remains the most important cause of fever. Thus, the initial investigations should always include tests for that purpose in a case of PUO. Geographic variations and local infection profiles should always be considered when investigating a case of PUO.⁵

More recently in Nizam Institute of Medical Sciences (NIMS),¹ hundred cases of classic FUO were evaluated in 10 years, 64 were males and 36 were females. The age range was from 18-70 years with peak incidence is 30-40 years.

Further breakup of each group was as follows-

Infection- TB 45, non-tuberculosis 15.

Among the patients with tuberculosis, 10 were disseminated, 12 were lymph nodal, 7 were Pott's disease, 5 were intestinal, 4 were renal and 7 were pericardial. Among no tubercular aetiology, 3 were brucellosis, 2 rickettsial, 5 protozoa (*falciparum* malaria), infective endocarditis 2, fungal 2 and viral 1 (CMV).

Collagen vascular diseases- Out of 24 collagen vascular diseases, SLE 14, adult Still's disease 4, polymyalgia rheumatica 2, MCTD 2 and polyarteritis nodosa 2.

Neoplasms- Among the neoplasm, lymphoma 8, renal cell carcinoma 2. Miscellaneous- Among miscellaneous, sarcoidosis 2, granulomatous hepatitis 1, LA myxoma and drug fever 2.

SUMMARY OF RESULTS

- The present study included 34 patients with pyrexia of unknown origin in which the patients' age ranged from 15 years to 77 years.
- Most of the cases, 41.2% were in the age group 21 to 40 years and 35.3% in the age group 41 to 60 yrs. This indicates PUO is common in middle age group in our study.
- Males were more commonly affected than females.
- 64.7% of the patients are males and 35.3% are females.
- 28 patients (82.4%) had no significant positive findings on general physical examination. Out of 34 patients with PUO, only 6 patients (17.6%) had significant findings on general physical examination.
- On systemic examination, only 9 subjects had significant positive respiratory findings and only 3 subjects had per abdomen tenderness and 1 subject had palpable spleen on examination. None of the patients had significant positive findings on neurological or cardiovascular examination.
- In our study, preliminary investigations like haemogram with peripheral smear, urine analysis, blood and urine C/S studies, chest x-ray and USG abdomen were normal in most of the patients.
- On haemogram and blood analysis, 17.6% had leucopenia, 26.5% had leucocytosis and 5.8% had thrombocytopenia. It was normal in all other patients.
- Urine analysis was normal in 28 (82.4%) of the patients, only 4 subjects had albuminuria and 2 had pus cells.
- In the culture sensitivity studies, culture (blood, urine or sputum) did not show any significant growth in most of the patients, 30 of 34 patients (88.2%).
- Smear for malarial parasite, Weil-Felix, Widal, Typhidot IgM and ANA were done for all the 34 patients. Out of which only one subject was positive in MP smear for *P. vivax* and ANA positive respectively and 4 subjects were

positive for Widal test, Typhidot IgM and Weil-Felix test, respectively.

- Out of the 34, 29 patients (85.3%) had normal chest x-rays and 21 patients (61.8%) had no positive findings on USG abdomen. Only 5 patients (14.7%) had positive findings on chest x-ray and 13 patients (38.2%) had positive findings on USG abdomen.
- CT and MRI studies were done in 5 of the 34 patients in the current study. Of which, these studies helped with the diagnosis in 2 patients (5.8%).
- FDG PET - CT scan was done in one of the 34 patients in our study. Though the scan did not reveal any diagnostic clue in this case, it is done as a part of the diagnostic workup to establish a diagnosis.
- In the current study of 34 patients of PUO, diagnosis could be made in 23 patients (67.6%) and despite the adequate workup diagnosis could not be made in the other 11 patients (32.4%).
- Infectious diseases were found to be the leading cause of the PUO. 22 of the 34 (64.7%) patients in the study were diagnosed with the infectious diseases.
- Among the infectious causes, enteric fever was the most common cause. 5 subjects (14.7% of PUO) had enteric fever.
- Among the other infectious causes, 4 subjects (11.8% of PUO) had rickettsial fever and tuberculosis, respectively; 3 subjects (8.8% of PUO) had HIV, 2 subjects (5.9% of PUO) had brucellosis and 1 subject had dengue, malaria and UTI (2.9% each), respectively.
- Only 1 patient was diagnosed with noninfectious cause. This patient was diagnosed to have Still's disease.
- In the current study, none of the patients had neoplasms as the cause for PUO.

CONCLUSION

One of the problems most frequently encountered in medical practice is the diagnosis of prolonged fever with or without local signs of disease.

Pyrexia of unknown origin continues to be a clinical condition, which defies technical advances in diagnostic modalities and the expertise of the clinical physician.

This problem perplexes both the physician and the patient. It is important to realise PUO may represent uncommon manifestation of common disease. Hence, the workup should be cost effective and thoughtful and clinically appropriate. Noninfectious causes like collagen vascular disease and neoplasms are becoming important differential diagnosis. But, in India, infections like tuberculosis, enteric fever are still the most common cause of FUO.

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