

Original Research Article

Clinical and etiological spectrum of prolonged fever and special reference to HIV patients at a tertiary care centre

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Received: 06 May 2018

Revised: 21 May 2018

Accepted: 24 May 2018

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ABSTRACT

Background: Prolonged fever is a diagnostic challenge and will tend to remain so in times to come because of the changing spectrum of etiologies and influence of technology, environmental changes, and many other ill-understood factors which influence the etiological spectrum. Prolonged fever is also undergoing change in its duration. The aim of the present was study to determine the etiologies of prolonged fever in patients in India and to evaluate the clinical and etiological relationship between the diagnosis and patient's laboratory data.

Methods: Patients aged more 13 years with fever >38.3°C for more than three weeks without apparent source after preliminary investigations were included prospectively over a period of twenty two months. Fever duration, symptom, signs, laboratory investigations and final diagnosis were recorded. The distribution of etiologies and age, fever duration, laboratory examinations, and associated symptoms and signs were analyzed.

Results: Out of total of 86 patients were enrolled, fifty one (59.3%) were men. The median age was 28 years (range, 13-65 yr). Among 86 patients, diagnosis could be made in only 69 (80.2%) patients. Infections, neoplasms, NIIDs, miscellaneous causes were responsible for prolonged fever in 42 (48.8%), 18 (20.9%), 6 (7%), and 3 (3.5%) patients respectively. Seventeen (19.8%) cases remained undiagnosed, even after relevant investigations, six of them recovered spontaneously. Tuberculosis (TB) was the cause of prolonged fever in 21 (24.4%) patients.

Conclusions: Infections, amongst which tuberculosis, remain the major cause of prolonged fever and its subset: fever of unknown origin (FUO), in this country. The percent of undiagnosed cases appears to be identical worldwide.

Keywords: Fever, Human Immunodeficiency Virus (HIV), Neoplasm, Tuberculosis

INTRODUCTION

Prolonged fever is a diagnostic challenge and will tend to remain so in times to come because of the changing spectrum of etiologies and influence of technology, environmental changes, and many other ill-understood

factors which influence the etiological spectrum. Prolonged fever is also undergoing change in its duration. Presently any fever for more than three weeks is called as prolonged fever.¹ But there is a strong contention to shorten the duration to two weeks. In the developing world infections still remain the major etiologies for prolonged fever while in the developed countries non-

infectious causes especially inflammatory causes are emerging as the major diagnostic category.²

Fever of unknown origin (FUO), a subset of prolonged fever is also undergoing changes in a similar way as mentioned above.³⁻⁶ Now the latest definition of FUO by Durack and Street brings in a sense of urgency in the diagnosis, which may tend to heighten the problem in developing countries like ours without having any effect on the final outcome on the patients. Hence it may be necessary to customize such definitions demographically. Prolonged FUO (≥ 3 weeks) should be reserved for cases that fulfill the Petersdorf-Beeson criteria as modified by Durack and Street, with the added qualification that the cause remains obscure after the results of all initial studies including cultures, serology, and imaging procedures have become available.⁷

METHODS

Keeping the above scenario in mind, it was preferred to study prolonged febrile illnesses and not specifically FUO (fever of unknown origin) only. The present study was a prospective observational study at a tertiary care centre in India. Patients who were aged ≥ 13 years and admitted under the Department of Medicine with a diagnosis of prolonged fever were screened over a period of two years. For inclusion into the study, the duration of fever at admission was required to be more than three weeks and documentation of temperature $\geq 38.3^{\circ}\text{C}$ ($>101^{\circ}\text{F}$) was needed on three or more separate occasions.

All patients who satisfied the inclusion criteria were studied. A complete history and physical examination based on a standard Proforma was done and a clinical diagnosis was ascertained. Patients were then subjected to appropriate and relevant investigations after which a final diagnosis was ascertained. Based on the diagnosis they were categorized (vide algorithm). Those patients who remained undiagnosed were subjected to special investigations/ follow up.

Once a diagnosis was ascertained in them, they were being categorized as above. In those for whom no diagnosis was achieved at the end of follow - up were categorized as unknown etiology (undiagnosed). All patients were further analyzed at the end of the study according to their HIV status. Finally, all patients were divided into two groups based on HIV status and their etiological profile was analyzed.

Statistical analysis

The statistical evaluation of the data obtained was done by expressing the continuous variables as median with range and discrete variables as percentage. The Chi-square test was used to examine the significance of difference between proportions.

There were 102 patients admitted in the department of internal medicine, JIPMER between September 2004 and July 2006 having history of fever for more than 3 weeks were listed in the study. 86 met the necessary inclusion criteria and included into the study. 16 patients were excluded, because in 2 patients temperature did not go above 38.3°C (101°F) on any occasion, 2 patients left the hospital against medical advice before diagnosis could be made, 11 patients died within two days of admission before diagnosis could be achieved, and 1 patient died on day 7 without fever documentation.

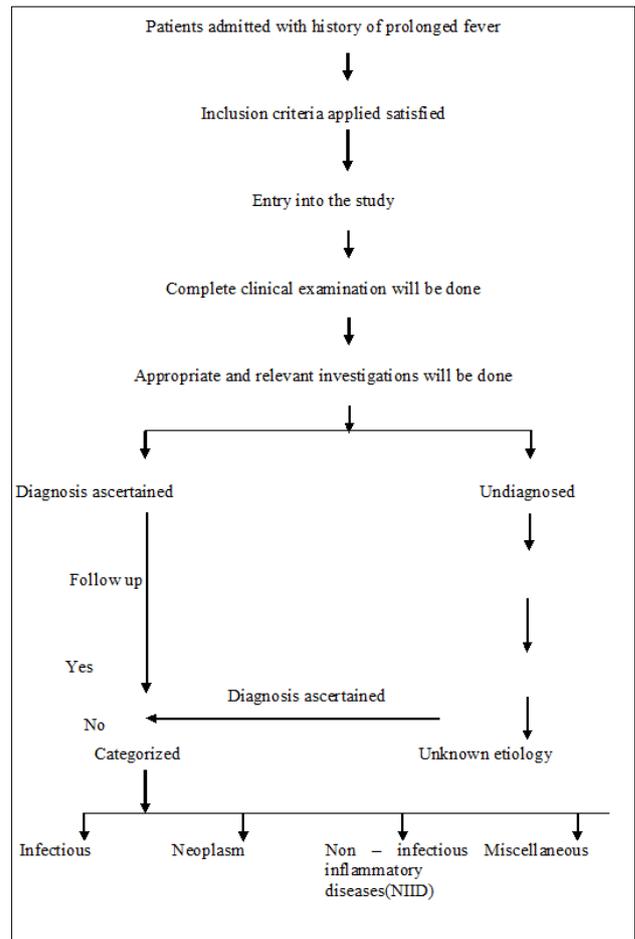


Figure 1: Graphical presentation of admitted patients.

RESULTS

Age and gender distribution

Out of 86 patients, 51 (59.3%) were men and 35 (40.7%) were women. The median age was 28 years (range, 13-65yr). There were 59 (68.6%), 25 (29%) and 2 (2.3%) cases in age groups 13-39, 40-59 and ≥ 60 years respectively. In 13-39 years age group, infections were found in 30 (50.8%) patients, neoplasms in 11 (18.6%), NIIDs in 6 (10.2%) and miscellaneous causes in 2(3.4%) (Figure 2). No diagnosis achieved in 10 (17%) cases. Among 40-59 year age group, infections were found in 12 (48%) patients, neoplasms in 7 (28%). No diagnosis

achieved in 6 (24%) cases. No patients had NIIDs or miscellaneous causes responsible for prolonged fever. Out of 2 patients in the age group ≥ 60 years, one had miscellaneous cause (Stevens-Johnson syndrome) and in the other no diagnosis could be achieved.

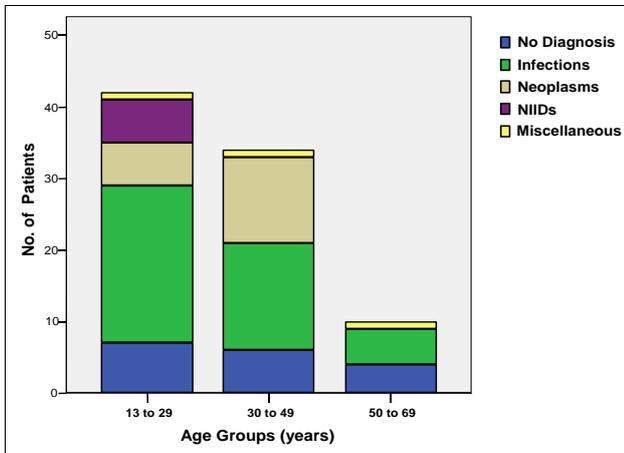


Figure 2: Age wise distribution of diagnostic categories in prolonged fever patients.

Fever

Out of 86 patients having prolonged fever, 71 (82.5%) patients were having fever for <3 months, 12 (14%) patients were having for more than 3 months but less than 6 months and 3 (3.5%) patients for more than 6 months but less than 1 year. No patient had fever for >1 year (Figure 3).

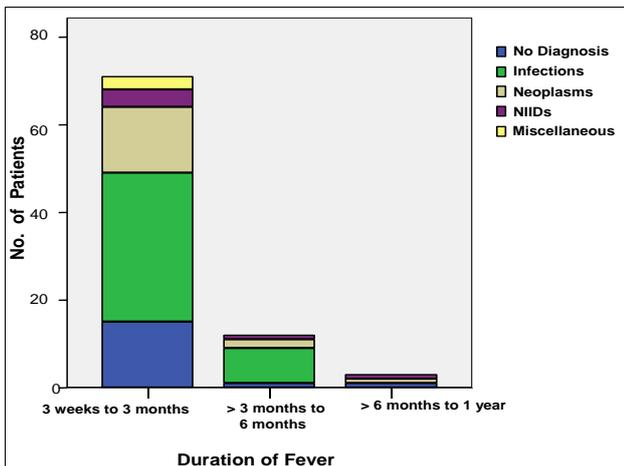


Figure 3: Diagnostic categories according to duration of prolonged fever.

Among the patients with fever duration 3 wks to 3 months, infections were diagnosed in 34 cases (47.9%), neoplasms in 15 (21.1%) cases, NIIDs in 4 (5.6%) cases and miscellaneous causes in 3 (4.2%) cases. In 15 (21.1%) cases no diagnosis could be made. Among 3-6

months fever group, 8 (66.6%) cases of infection, 2 (16.6%) cases of neoplasm and 1(8.4%) case of NIID were diagnosed. 1 (8.4%) case remained undiagnosed. Among 6 months to 1 year fever group, 1 (33.3%) case each was due to neoplasm and NIID. No diagnosis achieved in 1(33.3%) case. There were no cases having infections or any miscellaneous cause (Figure 4).

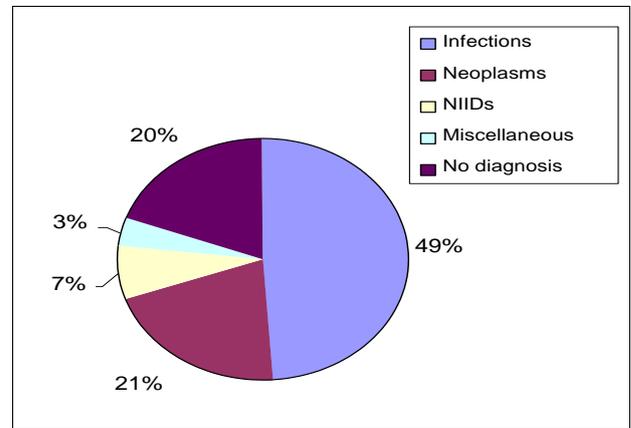


Figure 4: Prolonged fever diagnostic categories.

There were 73 patients (84.9%) had intermittent fever, 4 (4.6%) had continued fever and 2 (2.3%) had remittent fever, 7 (8.1%) patients presented with relapsing fever.

Among 86 patients of prolonged fever, 34 patients had highest temperature <101.9°F, 31 patients had <102.9°F, 15 patients had <103.9°F, 6 patients had <104.9°F, Among 35 patients of FUO, 13 patients had highest temperature 101.9°F, 16 patients <102.9°F, 5 patients <103.9°F, 1 patient <104.9°F.

Peripheral lymphadenopathy

Among 86 patients of prolonged fever, 25 (29%) had peripheral lymphadenopathy. In only 10 cases (40%), lymph node enlargement helped in diagnosis after FNAC or biopsy (In one case of lymphadenopathy, toxoplasma was suspected after FNAC and diagnosis was proved by serology). In rest it was nonspecific inflammatory enlargement of lymph nodes.

Potentially diagnostic CLUES (PDCs)

Potential diagnostic clues (PDCs) are defined as the localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis.

PDCs were helpful but not misleading in 42 (48.8%) patients and PDCs were misleading but not helpful 16 (18.6%) patients. In 14 (16.3%) patients, both helpful and misleading PDCs were present. No PDCs were there in 14 (16.3%) patients (Table 1). There was a significant difference (p= 0.005) in reaching the diagnosis between patients with clues (86%) and patients without clues (50%) (OR=6.20, 95% CI=1.53 - 25.83).

Table 1: Etiological spectrum of prolonged fever.

Prolonged fever	No of patients (n=86)
Infections	42 (48.8)
Tuberculosis	21 (24.4)
Pneumonia	3 (3.5)
Enteric fever	3 (3.5)
Pyogenic meningitis	3 (3.5)
UTI	2 (2.3)
Infective endocarditis	2 (2.3)
Renal abscess	1 (1.2)
Toxoplasma	1 (1.2)
Cryptococcal meningitis	1 (1.2)
Necrotizing fasciitis	1 (1.2)
Puerperal sepsis	1 (1.2)
Brucellosis	1 (1.2)
Cerebral malaria	1 (1.2)
Multiple myeloma, sepsis	1 (1.2)
Neoplasms	No of patients (n=18)
Hematological	
Leukemias	7 (8.1)
AML M2	4 (4.6)
AML M3	1 (1.2)
AML M5b	1 (1.2)
ALL L2	1 (1.2)
Lymphomas	6 (7)
NHL	4 (4.6)
Hodgkin's disease	2 (2.3)
Solid	5 (5.8)
Metastatic adenocarcinoma liver	2 (2.3)
Abdominal metastasis, germ cell tumour	1 (1.2)
Liver metastasis, g.i. stromal tumour	1 (1.2)
Epithelioid angiosarcoma	1 (1.2)
Non infectious inflammatory diseases (NIIDs)	6 (7)
Systemic lupus erythematosus	4 (4.6)
Still's diseases	1 (1.2)
Polyarteritis nodosa	1 (1.2)
Miscellaneous causes	3 (3.5)
Glucose 6 phosphate dehydrogenase deficiency	1 (1.2)
Paroxysmal nocturnal hematuria	1 (1.2)
Stevens Johnson syndrome	1 (1.2)

Detailed history and thorough clinical examination was decisive in 19 (22%) patients and helpful for further evaluation in 39 (45.3%) patients. By clinical re-evaluation, new helpful PDCs developed in 7 (8.1%) patients.

Microbiologic culture and serology

Among 86 patients of prolonged fever, culture helped in diagnosis of 3 (3.5%) cases, one case each of puerperal

sepsis due to *E. coli*, cryptococcal meningitis, and urinary tract infection due to *E. coli*. None of the blood cultures for *Mycobacterium tuberculosis* and fungi was positive.

Widal test was done in 35 patients. The test was positive in 5 patients. 3 cases (3.5%) responded to intravenous ceftriaxone, but cultures remained sterile. Because of the clinical picture and course, authors concluded that these patients had typhoid fever. But in other two cases clinical presentation was not like enteric fever and they did not respond to ceftriaxone, so we suspected positive Widal test to be an anamnestic reaction. Toxoplasma serology was performed in 13 patients. In one patient with generalized lymphadenopathy, toxoplasma serology (IgM) was positive. In 34 patients brucella serology was done. One patient who presented with typical clinical features suggestive of brucellosis, initially serology for brucellosis came negative. But because of high index of suspicion, when the serology was repeated with higher dilution (1 in1280) the test became positive. Initial negative result was due to prozone phenomenon. Leptospira serology, Paul-Bunnel test, VDRL test, filaria serology, and dengue serology were done in 13, 14, 2, 3, and 1 patients respectively; all tests were negative. Out of 26 Weil-Felix tests done 25 tests were negative and one test was false positive in a post partum lady presented with puerperal sepsis. HBsAg viral marker was positive for a patient, who presented with TB abdomen, but liver function tests were normal and we concluded that prolonged fever was not due to hepatitis. HIV test (ELISA) was done in all patients (86), 9 were HIV positive.

Biopsy

Biopsy helped in establishing diagnosis in 12 (14%) cases: lymph node biopsy in 5 cases (5.8%), bone marrow biopsy in 4 (4.6%) cases, liver biopsy in 2 cases (2.3%) (In one case liver biopsy was taken postmortem), and biopsy of the abdominal mass after laparotomy in one case.

Cytology /FNAC

Cytology (FNAC) was helpful in establishing diagnosis in 7 cases (8.1%). USG abdomen guided FNAC of abdominal lymph nodes/mass established diagnosis in 2 cases of metastatic adenocarcinoma of unknown primary and one case of NHL. Bone marrow aspiration cytology proved diagnosis in a case of Burkitt's lymphoma and a case of AML M2. One case epithelioid angiosarcoma was diagnosed by FNAC of a lump over the scalp. One case of TB lymphadenopathy was diagnosed by showing acid fast bacilli in FNAC of axillary lymph node.

Immunological tests

Antinuclear antibodies were helpful in establishing the diagnosis of systemic lupus erythematosus (SLE) in 3 cases. Immunochromatography helped in diagnosis of a

case of cerebral malaria. One case of paroxysmal nocturnal hemoglobinuria (PNH) was diagnosed after detecting deficiency of CD55 and CD59.

Biochemical tests

These tests helped in achieving diagnosis of 2 cases. A case of glucose 6 phosphate dehydrogenase deficiency which was responsible for hemolysis and fever was diagnosed by a biochemical test. The diagnosis of TB pleural effusion was established after getting high levels of pleural fluid adenosine deaminase (ADA).

Tuberculin (Mantoux) test

Mantoux test was done in 34 patients. The test was positive in only 3 patients- one each of disseminated TB, TB osteomyelitis and TB pleural effusion. None of them were HIV positive.

Imaging techniques

Standard radiology

Chest x-Ray was helpful in establishing diagnosis in 3 cases. One case each of lung abscess, millitary tuberculosis and pneumonia. X-Ray also contributed in reaching diagnosis in 8 cases. 2 cases of TB osteomyelitis (head of femur in one case and dorsal spine in other) were suspected from x-Ray study; both responded to empirical antitubercular therapy (ATT). Chest x-Ray revealed TB pleural effusion in 2 cases.

Ultrasonography (USG)

Ultrasonography established the diagnosis in 3 cases – one case of renal abscess, two cases of abdominal tuberculosis (one of which was disseminated tuberculosis). Abdominal ultrasonography contributed in reaching the diagnosis in 8 cases by showing pathological changes in liver and/or spleen and abdominal lymphadenopathy (two cases of NHL, one Hodgkin's disease, one Burkitt's lymphoma and 4 cases of solid abdominal tumours) out of these 8 cases, USG guided FNAC of abdominal lymph node was done in 3 cases to reach the diagnosis.

Computed tomography (CT)

In a case of toxoplasma lymphadenopathy without any neurological complaints, CT scan of brain was normal. In two cases of pyogenic meningitis CT scan was done; in one case there was infarction of left caudate lobe and in the other it was normal study. In three cases, CT abdomen showed same findings as of ultrasonography (one case each of left renal abscess, retroperitoneal mass and disseminated TB). CT was helpful in staging a case of Burkitt's lymphoma as it showed skull and orbit infiltration by lymphoma.

Magnetic resonance imaging (MRI)

In a case of brucellosis with severe low back ache and local spinal tenderness, MRI showed inflammation of the disc between fifth lumbar and first sacral vertebrae with paraspinal fluid collection.

Transthoracic echocardiography

Transthoracic echocardiography was helpful in finding one case of infective endocarditis and one case of aortic root abscess. We have not used trans-esophageal echocardiography for any of the patients.

Decisive method of diagnosis

Clinical course led to the diagnosis in 19 (27.5%) patients. 12 (17.4%) patients were diagnosed by biopsy, 7 (10.1%) by cytology, 3 (4.3%) by culture, 3 (4.3%) by serology, 7 (10.1%) by immunology, 3 (4.3%) by standard radiology, 3 (4.3%) by ultrasonography, 2 (2.9%) by echocardiography, 5 (7.2%) by smear, and 2 (2.9%) by biochemical tests respectively. Clinical judgment and investigations combinedly lead to the final diagnosis in 3 (4.3%) patients. 17 patients remained undiagnosed even after clinical reevaluation and relevant investigation.

Final diagnosis

Among 86 patients, diagnosis could be made in 69 (80.2%) patients. Infections, neoplasms, NIIDs, miscellaneous causes were responsible for prolonged fever in 42 (48.8%), 18 (20.9%), 6 (7%), and 3 (3.5%) patients respectively (Table 1). 17 (19.8%) cases remained undiagnosed, even after relevant investigations, 6 of whom recovered spontaneously.

Infections

Tuberculosis (TB) was the cause of prolonged fever in 21 (24.4%) patients: disseminated TB 8 (9.3%) TB lymphadenopathy 3 (3.5%), pulmonary TB 2 (2.3%), abdominal TB (intestinal TB, hepatic TB) 3 (3.5%), TB osteomyelitis 2 (2.3%), TB meningitis 1 (1.2%).

Pneumonia was diagnosed in 3 (3.5%) patients, enteric fever in 3 (3.5%) patients, pyogenic meningitis in 3 (3.5%) patients, urinary tract infection in 2 (2.3%) patients, and infective endocarditis in 2 (2.3%) patients. One case each of puerperal sepsis, necrotizing fasciitis, renal abscess, cryptococcal meningitis, acute toxoplasma lymphadenopathy, brucellosis, cerebral malaria and multiple myeloma with sepsis was also found.

Neoplasms

18 patients had neoplasms as the cause of fever: 13 had hematological and 5 had solid. Hematological malignancies were AML M2 (4 cases), AM2 M3 (1 case), AML M5b (1 case), ALL L2 (1 case), NHL (4

cases), and Hodgkin’s disease (2 cases). Among solid organ neoplasms, 2 cases metastatic adenocarcinoma of abdomen, and one case each of germ cell tumour, gastrointestinal stromal tumour and epithelioid angiosarcoma were diagnosed.

Noninfectious inflammatory diseases (NIIDS)

NIIDs were responsible for prolonged fever in 6 patients: SLE (4 patients), one case each of adult Still’s disease and polyarteritis nodosa (Table 1).

Miscellaneous causes

Miscellaneous causes were: ongoing hemolysis due to glucose 6-phosphate dehydrogenase deficiency, paroxysmal nocturnal hematuria, and Stevens Johnson syndrome - one case in each diagnosis.

Out of 33 patients of FUO, infections in 10 (30.3%), neoplasms in 6 (18.2%), NIIDs in 4 (12.1%) and miscellaneous causes in 2 (6%) were found out. 8 out of 10 infections were due to tuberculosis. No diagnosis could be achieved in 11(33.3%) patients (Table 2).

Table 2: Etiological spectrum of FUO (Petersdorf and Beeson).

FUO	No of patients (n=33)
Infections	10 (30.3)
Tuberculosis	8 (24.2)
Renal abscess	1 (3.0)
Enteric fever	1 (3.0)
Neoplasms	6 (18.2)
Hematological	2 (6.0)
AML M5b	1 (3.0)
NHL	1 (3.0)
Solid	4 (12.1)
Metastatic adenocarcinoma abdomen	2 (6.0)
Abdominal metastasis, germ cell tumour	1 (3.0)
Epithelioid angiosarcoma	1 (3.0)
Non infectious inflammatory diseases(NIIDs)	4 (12.1)
Systemic lupus erythematosus	2 (6.0)
Adult Still’s disease	1 (3.0)
Polyarteritis nodosa	1 (3.0)
Miscellaneous causes	2 (6)
Glucose 6 phosphate dehydrogenase deficiency	1 (3.0)
Paroxysmal nocturnal hematuria	1 (3.0)

Prolonged fever in HIV positive patients

There were 9 patients out of 86 patients of prolonged fever had HIV serology positivity. All of them were

diagnosed first time to be HIV positive during the index admission for prolonged fever.^{8,9}

Prolonged fever was due to infection in 7 (78% of HIV positive patients) cases and drug induced Stevens-Johnson syndrome in one case; one case remained undiagnosed (Table 3). We did not get any case of neoplasm in HIV positive patients presenting as prolonged fever. Among 7 cases of infections, diagnoses were tuberculosis in 5 cases, cryptococcal meningitis in one case, and pneumonia in one case.

Table 3: Prolonged fever in HIV -ve and +ve patients.

	HIV negative patients (n=77)	HIV positive patients (n=9)
Median age (years)	27	33
Gender		
Men	42 (54.5)	9 (100)
Women	35 (45.4)	0 (0)
Diagnostic category		
Infections	35 (45.4)	7 (77.7)
Neoplasms	18 (20.9)	0 (0)
NIIDs	6 (6.9)	0 (0)
Miscellaneous	2 (2.6)	1 (11.1)
No diagnosis	16 (20.7)	1 (11.1)
FUO	32 (41.5)	1 (11.1)

Only one HIV positive patient was fitting into the Petersdorf and Beeson criteria of FUO for whom diagnosis could not be made.

FUO (Fever of Unknown origin)

In this study, infection (30.3%), predominantly TB (24.2%) was the most common diagnostic category. We tried to apply Durack and Street criteria to redefine FUO. In this study of total 86 cases of prolonged fever, 69 cases satisfied the criteria of FUO. Infections consisted 34 cases (49.3%), neoplasm 13 cases (18.8%), NIIDs 6 cases (8.7%) and miscellaneous causes 3 cases (4.3%). 14 (20.3%)cases remained undiagnosed.

The 3 day period, as proposed by Durack and Street represents, in fact, the time needed for classical cultures and skin tests to become positive. The serological and immunological studies and the required imaging if indicated can be performed in 1 day or after one outpatient visit. This change reflects the evolution of modern medicine, with more emphasis on outpatient investigation and a much higher pace of in-hospital investigation. However, 3 outpatient visits cannot be considered equivalent to 3 days in-hospital investigation, mainly because of the longer time interval in the outpatient approach, moreover all available investigations cannot be done at admission to get the results within 3 days, because it is not cost effective. Careful observation and relevant investigations according to emerging PDCs

is a more reasonable approach particularly in developing countries like ours. So, authors found that the Durack and Street criteria of FOU amplified the diagnosis unnecessarily without having any impact on the management. The proportions of FOU according to Petersdorf-Beeson criteria and Durack-Street criteria were significantly different ($p < 0.001$), as the majority of patients with prolonged fever satisfied the later criteria (Table 4).

Table 4: Diagnostic categories in patients with prolonged fever and FOU.

Diagnostic category	Prolonged fever (n= 86)	Fever of unknown origin- Petersdorf & Beeson (n=33)	Fever of unknown origin- Durack & Street (n=69)
Infections	42(48.8)	10(30.3)	34(49.3)
Neoplasms	18(20.9)	6(18.2)	13(18.8)
Noninfectious inflammatory diseases (NIIDs)	6(7.0)	4(12.1)	6(8.7)
Miscellaneous	3(3.5)	2(6.0)	3(4.3)
No diagnosis	17(19.8)	11(33.3)	13(18.8)

Mortality

In this study 3 patients died during hospital stay due to FOU related causes: one case each of gastrointestinal stromal tumour with liver metastasis, multiple myeloma with sepsis, and adult Still’s disease. According to published literature, overall, 12% to 35% of patients die from FOU-related causes; with malignancies incurring the highest mortality. None of our patients in whom we could not reach a definite diagnosis died. Most of them had spontaneous recovery. Previous studies also state that prognosis of patients with FOU in whom a cause cannot be identified is excellent.

DISCUSSION

In this study, infection was the most common diagnostic category responsible for prolonged fever; constituting almost half of the population.

According to series from university hospitals the frequency of infections and tumours has declined during the last decade, whilst NIID and the number of undiagnosed cases have increased, when compared with earlier studies.¹⁰⁻¹² This shift of distribution of disease categories is probably due to routine use of new diagnostic techniques such as ultrasonography in the detection of intra abdominal abscesses, CT scan in search for lymphomas and solid tumours, trans-esophageal echocardiography for the diagnosis of endocarditis and

scintigraphy methods in patients without having any localizing clinical features.

Infections still remain the most common etiologic group in recent series reported from community hospitals and from developing countries. Indian studies from tertiary centers have shown infection to be the most dominant diagnostic category.¹³

The most common infections cause in this study was tuberculosis which is in agreement with literature study.

Most common malignancies responsible for prolonged fever in this study were hematological malignancies. But the most common malignancies causing FOU in this study were intra abdominal solid organ malignancies (metastatic adenocarcinoma of abdomen with unknown primary). This was because most of the hematological malignancies could be diagnosed within one week. In the Petersdorf and Beeson study and De Kleijn et al. study, however, the most common malignancies presenting as FOU were hematological (lymphomas).

Geographic factors, age distribution of the study population, referral pattern, hospital setting, and time and duration of study influence the distribution of diagnostic categories.^{14,15}

Algorithmic and staged diagnostic approaches reported in the literature are experience based. No uniformly useful diagnostic algorithm can be constructed, because the etiologic spectrum changes not only from time to time but also from place to place. One problem with standard diagnostic protocol is that it may result in too many unnecessary tests.¹⁶ Algorithm may be useful when no PDCs are found or when clinician is less experienced. PDCs reduce the number of unnecessary investigations. Every effort should be made to find out PDCs. A reasonable and cost-effective alternative to algorithm in patients without PDCs would be re-evaluation clinically after a specified period.

Limitations of the study includes since the socioeconomic strata of patients attending government hospitals are confined, the spectrum of diseases may be a close approximation of the society in general and most of the undiagnosed cases were lost to follow up. So, long term outcome of these cases could not be made.

CONCLUSION

A total of 86 patients with prolonged fever were studied and diagnosis could be made in 69 (80.2%) patients, of whom 42 (48.8%) had infections, 18 (20.9%) had neoplasms, 6 (7%) had noninfectious inflammatory diseases (NIIDs), and 3 (3.5%) had miscellaneous causes. No diagnosis could be made in 17 (19.8%) patients, 6 of whom recovered spontaneously. Tuberculosis was the most common infectious cause of prolonged fever (24.4%). Most of these mycobacterial infections were

extrapulmonary. The median age was 28 years (range, 13- 65 yr) with only 2 patients above age 60 years. 51 (59.3%) were men and 35 (40.7%) were women. Fever was low grade (temperature < 103°F) and vital parameters were well preserved in the vast majority. Generalized lymphadenopathy as compared to localized lymphadenopathy was a more helpful PDC. The likelihood of reaching a diagnosis in patients with PDCs was significantly higher than in patients without PDCs. Biopsy was the most rewarding technique in this study. Biopsy of lymph node and bone marrow in particular provided high diagnostic yield. The screening value of microbiologic serologies and immunologic tests was nil; these investigations probably should be performed only when PDCs for the disease searched for are present. Amongst the imaging techniques, ultrasonography was most useful for work up of prolonged febrile illnesses. Complete blood count overall was unhelpful except in suspected cases of leukemia. However, the finding of leucocytosis may suggest an infectious etiology. Most of the patients had high ESR, so did not have any diagnostic value. Empiric therapy with beta-lactam antibiotics may have little or no role in prolonged febrile illnesses. Shortening the duration of work up, as proposed by Durack and Street, amplified the problem of FUO. Tuberculosis was the most common cause of prolonged fever in both HIV positive and HIV negative patients. Infections continue to be the major diagnostic category in prolonged febrile illnesses.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Behera S, Subrahmanyam KS, Bajpai J, Pradhan A, Singh A. Clinical and etiological spectrum of prolonged fever and special reference to HIV patients at a tertiary care centre. *Int J Res Med Sci* 2018;6:2243-50.