ORIGINAL ARTICLE

Etiology of Classic Fever of Unknown Origin (FUO) among Immunocompetent Indian Adults

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Abstract

Background: Fever of unknown origin (FUO) has been a vexing problem for physicians for decades. The advent of imaging, functional scans, guided procedures and advanced molecular techniques has made many of the hitherto undiagnosed diseases easily diagnosable. FUO epidemiology can be geographically unique varying from country to region. Studies done in India are scarce, with variable definitions.

Methods: This prospective observational cohort study recruited 300 consecutive patients presenting with classic FUO as defined by Durack and Street. Potential diagnostic clues (PDCs) were identified and workup proceeded towards establishing a confirmatory diagnosis.

Results: Among the 300 classic FUO in our series, infections, neoplasms and NIIDs contributed to 48%, 21.6% and 20.6% of the cases. Tuberculosis and Melioidosis were the most important infections. Hematological malignancies like Non Hodgkins' lymphoma, Hodgkins' lymphoma and Leukemia contributed to 78% of neoplasms causing FUO whereas solid organ malignancies contributed to 18% of the cases. Among the NIIDs, Systemic lupus erythematosus, Granulomatous diseases and Vasculitis contributed to 26%, 18% and 14.5% respectively. Diagnostic tests of utility included image guided biopsies (100%); CT scan of abdomen and or thorax (92.4%) and Lymph node biopsies at 72%. Mortality was 5%. A boot strapping analysis was done on PDCs contributing to each specific diagnostic category and algorithms were developed.

Conclusions: This is the largest series of FUO from South India. Systematic sequence of investigations without start of empirical therapy led to a diagnosis in 99.4% which is the highest in described literature.

Introduction

Fever of unknown origin (FUO) has perplexed physicians for generations. The causes of FUO are more than 200 and detailed knowledge of various medical conditions is required to reliably make a diagnosis. Petersdorf and Beeson in 1961 in their original paper defined FUO as fever more than 38.3°C (101°F) on several occasions with a duration of greater than 3 weeks and uncertain diagnosis after 1 week of inpatient hospital investigations.[2] With the advent of HIV infection, organ transplantation and improvement of intensive care facilities this was subsequently revised by Durack and Street et al into 4 categories: Classic FUO, Neutropenic FUO, Nosocomial FUO and HIV associated FUO.[3] However despite the advances in diagnostic techniques and facilities the proportion of undiagnosed entities has continued to be substantial in the case of classic FUO.[4] The diagnosis and spectrum of FUO has been elucidated from the developed countries, but data from India and other developing countries is limited. The main causes of classic FUO include infections, neoplasms and Non infectious Inflammatory Diseases (NIID).[1] However in developing countries, infections are a prominent cause of FUO unlike in developed countries, where all three play an important role.[5] Therefore diagnostic approach in India to FUO has to be distinctly different from that in the developed countries considering the different spectrum and costs. FUO series from India have included data from East (Kolkata), West (Mumbai), Central (Wardha) and North India (Delhi) with no data from South India, hence this study was designed to prospectively evaluate classic FUO in a tertiary care hospital with a view to elucidating various causes of FUO, identifying potential diagnostic clues (PDC) and using these to develop an algorithmic approach applicable in a resource limited setting.

Material and Methods

This was a prospective observational cohort study performed over a 20 month period from December 2010 to July 2012, at Christian Medical College (CMC) Vellore, Tamil Nadu, India. CMC Vellore is a tertiary care hospital with patients across the country accessing care.

We enrolled patients (age > 15 years) who fulfilled the following criterion for classical PUO as defined by Durack and Street et al.[3]

Temperature of >38.3 degree C (101 degree F) on several occasions as documented by a health care practitioner for > 3 weeks duration and in whom there was a failure to establish a diagnosis with appropriate investigations after 3 outpatient visits or 3 days as an inpatient.

We excluded patients with HIV associated FUO, Neutropenic (< 500

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cells/mm^3) FUO and nosocomial FUO and those on steroids (> 10 mg/day) or other immunosuppressants for at least 2 weeks or those on chemotherapy for a malignancy. Moribund patients with PUO who were unlikely to survive the duration of diagnostic investigations were also excluded. Preliminary tests were done to exclude an acute febrile illness and then were recruited into the study.

Based on localizing clinical features, patients were then subjected to second rung of tests usually an imaging - Ultrasound Abdomen, CT Abdomen and Thorax (contrast-enhanced), CT or MRI brain/ spine. Analysis, aspiration, cultures and biopsies of fluid, collections and tissue were done if clinically indicated. Endoscopies with biopsies and cultures and PET scanning were also considered if required. All demographic and clinical variables were collected in a structured data form by the principal investigator. Repeated and detailed physical examinations were done every two days. We provided assistance to the investigation of FUO but no rigid protocol/algorithm was followed. The final diagnosis established at discharge or during follow-up comprised the main outcome of the study. Only diagnoses confirmed by a diagnostic test or sufficiently validated by a therapeutic trial with reasonable certainty were accepted. The laboratory test or diagnostic method that diagnosed the cause of fever first was also recorded. Tests were halted as soon as the diagnosis was established, and appropriate treatment initiated. Patients with empirical therapy were strictly monitored and followed up to ensure a sustained clinical response. If no diagnosis was obtained despite detailed and invasive evaluation on first admission and patients were clinically stable, they were counselled against empirical therapy and advised to come back for a re-evaluation after 6 weeks if symptoms persisted with the intention that the disease would have progressed enough for us to make a diagnosis.

Definition for disease states

Tuberculosis (TB) was diagnosed when M. tuberculosis grew in culture on tissue/tissue fluid or granulomas were seen on histopathology with a compatible clinical picture and a clinical response to antituberculosis therapy (ATT).

Occult tuberculosis was diagnosed when we were unable to obtain a tissue or culture diagnosis during that admission but was proven later by positive cultures for M. tuberculosis or a dramatic response to empirical ATT with clinical and radiological resolution.

Infective endocarditis was diagnosed when Modified Duke's Criteria were fulfilled.

Melioidosis was diagnosed based on growth of Burkholderia psuedomallei on culture from appropriate sample (pus, blood, urine).

Enteric fever was diagnosed when blood/bone marrow culture grew Salmonella typhi/paratyphi or WIDAL positivity with rising titres in a compatible clinical setting with response to treatment for enteric fever.

Rheumatoid arthritis diagnosis was made based on the 2010 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revision of the 1987 ACR classification criteria for RA.

Various rheumatological diseases were diagnosed based on their established criteria.

Lymphomas or haematological malignancies were diagnosed based on histopathology and Immunophenotyping from appropriate tissue.

Diseases as defined above with relevant clinical and laboratory features were noted and grouped into the three major etiological groups i.e., infections, neoplasms and non-infectious inflammatory diseases (NIIDs).

Sample size was calculated to be 96 based on the prevalence of tuberculosis of 40% (25-50%) among FUO studies in India

Sample size= $(1.96^2 \times P \times [1-P])/D^2$

P=prevalence of the disease (%), D= confidence interval (taken as 10%). Summary statistics and tests of significance (Chi square test for categorical variables and student t-test for continuous variables) were done using statistical software package SPSS version 16.

Institutional review board approval and funding

IRB approval was obtained prior to starting the study and funding was provided through an internal fluid research grant, to a post graduate student in Department of General Medicine and was subsequently submitted to the Tamilnadu Dr MGR Medical University as a PG dissertation.

Results

A total of 300 consecutive patients were recruited into the study. Almost 65% were male with an average age of 40 years (median 40; range 15-76 years). Two-thirds of our patients were from Tamil Nadu (31%) and West Bengal (32%) with the rest from South and North Indian states. The mean duration of fever prior to presentation was 148 days (median: 90; range- 21 to 1460).

Overall the striking clinical features included anorexia (58%) and weight loss (61%) in two-thirds, followed closely by pallor (41%) hepatosplenomegaly (33%) and lymphadenopathy (30%). A third (32%) of them had symptoms localizing to the respiratory tract i.e., cough and dyspnea and 12% localizing to the CNS - headache, seizures or focal deficits with the rest to the musculoskeletal system. Important localizing lab tests included elevated alkaline phosphatase (56.5%), and an abnormal chest X-ray (25%). Median Hb was 12.45. (Range: 3.6 -15.3), median ESR and CRP were 46 (range: 7-140) and 7 (range: 2-218), respectively.

In our cohort, infection was the most common cause of classic FUO accounting for 48% of all cases, followed by neoplasms in 21.6% cases and non-infectious inflammatory diseases in 20.6% of the cases. Miscellaneous and undiagnosed causes accounted for the remaining 8.6% and 1.6% of the cases.

Among the infections, tuberculosis in varied forms was the leading cause of infectious FUO accounting for 61% of the cases, followed by Melioidosis (10%), subacute bacterial endocarditis (4%) and visceral abscesses (4.8%), invasive fungal infections (3.4%), disseminated histoplasmosis (2.7%) and fungal endocarditis in 0.7%. Other causes accounted for 10% and included varied causes like delayed diagnosis of Enteric fever, Visceral leishmaniasis, Type II Lepra reaction, Brucellosis etc.

Among the tuberculosis patients, disseminated (45%), extra-pulmonary (33%) and pulmonary in 14% were the commonest clinical presentations with occult tuberculosis in 8% of the cases. Among the extra-pulmonary

Table 1: Distribution of specific categories of FUO across the age groups

Age group	Infection	Neoplasm	NIID	Miscellaneous	Total
<20 years	9	3	7	4	23
% within category	6.3	4.6	11.3	13.8	
% within age group	39.1	13	30.5	17.4	100
20-29 years	33	8	23	6	70
% within category	22.9	12.3	37.1	20	
% within age group	47.1	11.4	32.9	8.6	100
30-39 years	24	9	10	7	50
% within category	16.7	14	16.1	23	
% within age group	48	18	20	14	100
40-49 years	38	20	13	3	74
% within category	26.3	30.8	21	10	
% within age group	51.4	27	17.6	4	100
50-59 years	20	15	3	7	45
% within category	13.9	23	4.9	23	
% within age group	44.4	33.3	6.7	15.6	100
Above 60 years	20	9	6	3	38
% within category	13.9	13.8	9.7	10	
% within age group	55	23	15	7	100
Total	144	64	62	30	300

Table 4: Potential diagnostic clues in each category

	Infection	Neoplasm	NIID	P Value
Symptoms				
Cough	64.5%	24.8%	9.7%	0.019
Diarrhea	50%	0	50%	0.028
Headache	84.6%	0	15.4%	0.050
Arthritis	22.2%	2.8%	75%	0.000
Rash	9.5%	23.8%	66.7%	0.000
Signs				
Pallor	42.5%	38.1%	19.5%	0.000
Lymphadenopathy	38.4%	36%	25.6%	0.001
Hepatosplenomegaly	43.4%	45.3%	11.3%	0.000
Arthritis	22.2%	2.8%	75%	0.000
Basic investigations				
Anemia (Hb <8 g%)	58.1%	18.6%	23.3%	0.000
Thrombocytopenia	39.2%	45.1%	15.7%	0.000
Leukopenia (WBC count <4000 cells/mm.cu)	43.9%	39.0%	17.1%	0.044
Diagnostic tests				
Blood culture	100%	0	0	0.001
Bone marrow studies	34.9%	62.8%	2.3%	0.000
CT thorax	58.6%	13.8%	27.6%	0.019
CT thorax with abdomen	56.8%	32.4%	10.8%	0.006
Lymph node biopsy	50.0%	41.3%	8.7%	0.000

Table 2: Differential diagnoses of FUO in India

Diagnosis	No. of pts. (%)	% of specific diagnostic category
Infections	144 (48)	
Tuberculosis	88 (29)	61
Melioidosis	16 (5)	10
Infective endocarditis	6 (2)	4
Visceral abscesses	7 (2)	4.8
Disseminated histoplasmosis	4 (1)	2.7
Fungal endocarditis	1 (0.3)	0.7
Enteric fever	6 (2)	4
Visceral leishmaniasis	3 (1)	2
Lepra reaction	3 (1)	
Brucellosis	2	
Others (1 case each)*	8	
Neoplasms	64 (22)	
Non hodgkin's lymphoma	20 (7)	31
Hodgkin's lymphoma	17 (6)	26
Lymphoma unclassified	2	3
Leukemia	6 (2)	9
Multiple Myeloma	6 (2)	9
Solitary plasmacytoma	1	
Myelodysplastic syndrome	1	
Solid organ tumours	12 (4)	18
Non infectious inflammatory diseases	61 (21)	
SLE	16 (5)	26
Vasculitis	9 (3)	14.5
Inflammatory bowel disease	4	
Sarcoidosis	2	
Kikuchi's disease	5	
Mixed connective tissue disorder	5	
Still's disease	5	
Rheumatoid Arthritis	4	
Seronegative spondyloarthropathy	2	
Others**	9	
Miscellaneous	26 (8.6)	
Self limited	17 (5)	
Hyperthyroidism	6 (2)	
Others***	3 (1)	
Undiagnosed	5 (2)	

Table 3: Diagnostic yield of various tests in the diagnosis of FUO

Diagnostic test	Diagnostic yield (%)
Chest X-ray	25.3
Ultrasound abdomen	66.8
CT thorax and abdomen	83.2
Bone marrow aspiration, biopsy, cultures	18.5
Lymph node biopsies	69.6
PET scan	66.7
Liver biopsy	50
Diagnostic splenectomy	100

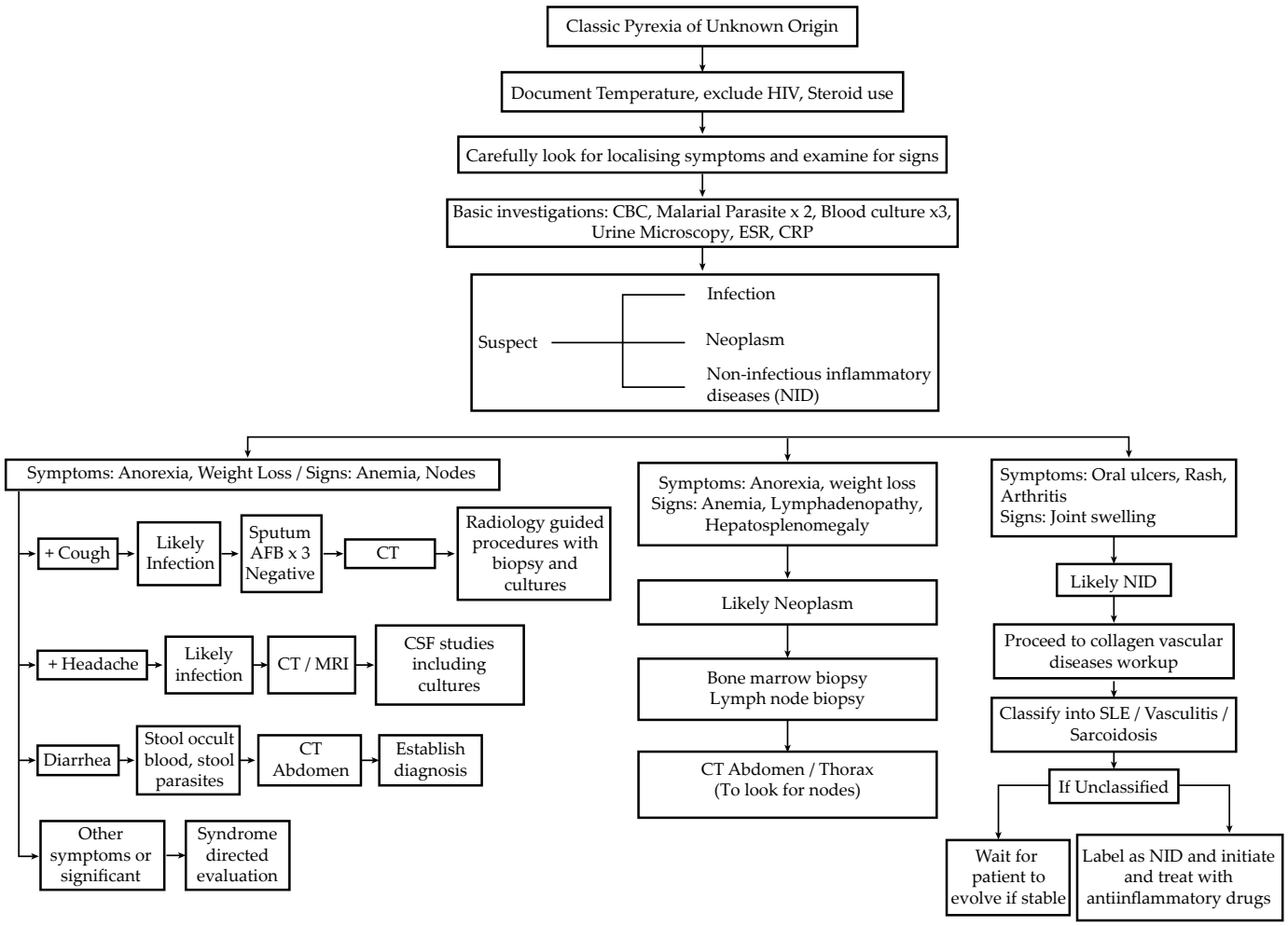
tuberculosis, meningeal and lymph nodes were the most common sites, accounting for 70% of the cases.

Melioidosis caused by *B. pseudomallei* emerged as the second most important cause of infection contributing to a PUO accounting for 10% of all infections and 5% of overall cases of FUO. The predominant risk factor for acquisition of Melioidosis was diabetes. The diagnosis was made from blood culture (septicemic melioidosis) in 37.5% and aspiration from visceral abscesses, bone or other sites (Chronic Granulomatous Melioidosis) in 62.5%. Infective Endocarditis (IE) and pyogenic abscesses (liver, spleen and renal) accounted for 2.3% of all cases. Among invasive fungal infections, disseminated histoplasmosis and fungal (Candida) endocarditis contributed to 1.6% of the causes of PUO.

Neoplasms caused FUO in 22% (n=64) of cases. Haematological malignancies were the commonest neoplasms accounting for 78% with lymphoma accounting for 60%, leukemias 9% and multiple myeloma 9%. Solid organ malignancies like colon, lung, prostate accounted for 18% (n=12) of FUO. Less common causes were hepatocellular and poorly differentiated carcinoma.

Non-infectious inflammatory diseases (NIID) caused classic FUO in 21% of the cases and among these, systemic lupus erythematosus (SLE) was the most common (26%) followed by vasculitis (14.5%), Mixed Connective Tissue Disease and Adult onset Still's disease at (8%). Other infrequent causes included Rheumatoid Arthritis, Kikuchi-Fujimoto disease, Seronegative Spondyloarthropathy, Inflammatory bowel disease and, Sarcoidosis.

Rarer causes of PUO, like hyperthyroidism, accounted for 2% of all cases. Among those fevers in which no cause could be found, 8.6% were self-limited and truly undiagnosed cases were seen in only 1.6% of the



Abbreviation: HIV: human immunodeficiency virus; CBC: complete blood count; ESR: erythrocytes sedimentation rate; CRP: C-reactive protein; CT: computerised tomography; MRI: magnetic resonance imaging; CSF: cerebro spinal fluid; SLE: systemic lups erythematous; AFB: acid fast bacilli

Fig. 1: Algorithm for diagnosis of classic FUO in India

entire cohort.

Infections were the most common cause of FUO across all age groups. In patients < 50 years, NIIDs were second most common (occurring in the third decade, between 20 to 29 years of age) but in patients > 50 years neoplasms were second (occurring in the 5th decade, between 40 -60 years). Infections were uncommon in the very young (< 20 years) (Table 1).

Invasive procedures were needed to make a diagnosis in 69% of the cases and image guided biopsies had the highest diagnostic yield 100% followed by lymph node and bone marrow biopsies with cultures at 63% and 19%. Non-invasive tests including CT scans, revealed a diagnosis in 72.4%. Diagnosis was made based on clinical picture alone in 3% of the cases.

We noted every symptom, sign or abnormal laboratory test that contributed to a specific diagnostic category and the final diagnosis. The variables which were seen in maximum proportion in a particular diagnostic category i.e., infections, neoplasms and NIIDs were then subjected to univariate analysis and the significant variables were noted. Potential diagnostic clues (PDCs) both clinical and laboratory in each specific diagnostic category (Table 4) were used to construct an algorithm for evaluation of classic FUO (Figure 1).

The mortality in this FUO series was 5% (n=15) and the commonest diagnosis among patients who expired was lymphoma or disseminated tuberculosis. Two patients died without a diagnosis ever being made.

Discussion

This is the largest prospective observational cohort study of classic FUO from South India. Most studies from developing countries show that infections are the most common cause of FUO,[6] and they accounted for 48% of cases in our series. Classic FUO in India is often also due to delayed diagnosis of acute febrile illnesses with lack of confirmation either through culture or molecular techniques and further compounded by lack of specificity of serology in an endemic setting. The previous studies elucidating the causes of classic FUO have used inconsistent and different definitions of disease processes thus questioning their validity and reliability.[7] In addition there can be varying causes of FUO depending on the geographical location and prevalence of local diseases and hence causes of fever are often different in East, West, North and South India.[7-10] We used very strict definitions of disease in our study validated in a previous published FUO study.[11]

Infections as the major category

of FUO has predominated over the decades and this has remained consistent[9,10] in India. In our study, Tuberculosis comprised 1/3 (29%) of all cases and 2/3 (61%) of the infections similar to previous Indian studies. In the latest case series described from Kolkata,[10] 28 % of the patients had tuberculosis with 72% having extra-pulmonary tuberculosis. In the series by Kejariwal et al,[9] tuberculosis was again the commonest diagnosis but pulmonary tuberculosis was not seen presenting as PUO unlike our series, where pulmonary tuberculosis was seen in 14% of the cases. In our studies, diagnosis was most often established from specimens other than sputum AFB smear or culture e.g., bronchoalveolar lavage, pleural fluid or molecular techniques.

Melioidosis was the second most common infection contributing to a classic FUO and this has not been described before as an important cause in previous studies. We feel that this is because though abscesses have been described in previous studies[9] as a common cause of FUO in previous studies, the etiological agent of Melioidosis i.e., Burkholderia Pseudomallei was probably not identified in these patients. Limited experience, lack of validated diagnostic strategies and dependence on automated blood systems often leads to misdiagnosis of this organism.[10] The Microbiology laboratory in our hospital has a standard protocol for identification based on typical morphology (closed safety pin appearance), appearance of culture plate (metallic sheen), oxidase negativity, testing with polyclonal antiserum (in house preparation of antiserum in rabbits) and resistance to Gentamicin and Polymyxin B on antimicrobial susceptibility. This organism is often dismissed as a contaminant as it is a non fermenting gram negative bacillus and on isolation from specimens from non sterile sites it may be overgrown by commensal organisms.[12,13] There has been a decrease in prevalence of endocarditis as a cause of FUO, probable to due to earlier recognition of the same due to better culture techniques and availability of Transoesophageal Echocardiography (TOE).

Among the neoplastic causes of FUO apart from haematological causes of malignancies, solid organ cancers also caused FUO. This is unlike what has been described from other case series. In fact, in the series by Bandyopadhyay et al,[10] solid organ cancers did not present as PUO.

Infections were the commonest cause across all age groups. There seemed to be a clear distinction between <50 years and >50 years for the second most common cause. NIID were common in the <50 years age group vs. neoplasms in >50 years age group. This seems to be different compared to what is seen in Western Literature where NIIDs were the commonest cause of FUO as compared to infections and neoplasms.[14] The number of undiagnosed cases in our series in one of the lowest in published literature and we attribute this to the fact that we are a tertiary care centre with all the facilities available on site and inclusion of only established and health care documented cases strictly documenting temperatures rather than just based on patient history, thus fulfilling the criteria of classic FUO. This low percentage of undiagnosed cases (1.6%) is in sharp contrast to all other case series so far, which have described undiagnosed cases between 7 to 51%.[5,15] Every attempt was made to obtain unequivocal confirmation of diagnosis by invasive or non-invasive means for e.g., diagnosis of an infection was based only on cultures in the background of a compatible clinical picture; diagnosis of a neoplasm was based on confirmatory histopathological and/or immuno-histochemical evidence. A diagnosis based on clinical judgement without conclusive microbiological or histopathological evidence was made in only 3.7 % of the cases and empirical therapy was instituted in these patients with close follow up to ensure that the initial diagnosis was correct. Only patients who had complete clinical and radiological resolution to empirical therapy consistent with the original clinical diagnosis were deemed to have that disease process. This was mostly limited to occult tuberculosis and undifferentiated collagen vascular disease.

On evaluation of various diagnostic tests, the following were found to have a diagnostic yield of >50% - diagnostic splenectomy (100%); CT thorax and Abdomen (83%), lymph node biopsy (70%), Ultrasound abdomen and PET scan (67% each) (Table 3). We found that imaging with guided biopsies were the mainstay of diagnosis. Our study suggested lymph node biopsies should be done early if lymphadenopathy is detected, with repeated screening for the same as these have a high diagnostic yield. Bone marrow biopsies though often done were found to have a fairly low diagnostic yield of 19%, similar to other series of FUO up to 25%[16,17] suggesting that they should only be a third rung of investigations. We found rare causes of PUO in our case series, likely due to the large sample size and diagnostic abilities.

Limitations include a possible referral bias; patients referred to us were usually evaluated elsewhere and referred after non-response to a therapeutic trial, leading us to suspect an alternate diagnosis. We were unable to conclusively establish a causal spectrum of FUO from South India alone, as our centre sees a large number of cases from Eastern India.

In conclusion, infections are most important cause of classical FUO with extrapulmonary tuberculosis being the most frequent, in India. Melioidosis is an emergent cause of FUO seen often in diabetics. Lymphoma is the commonest neoplasm FUO and SLE was the most common non-infectious inflammatory disease causing FUO. Invasive tests especially lymph node biopsy have a high diagnostic yield in FUO and hence patients should be referred to centres where these can be done in case of diagnostic dilemmas. The number of cases in our series who remained undiagnosed was extremely small as compared to previous studies, probably due to a strict documentation of fever in hospital, an aggressive diagnostic approach to FUOs and avoidance of empirical therapy as much as possible.

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