

Review Article:**Fever of unknown origin (FUO): evolution of case definition, changing aetiological spectrum****D. Prabhath Kumar, D. Arun Kumar, K. Rajeshwari, D. Neeharika, G. Sindhu, B. Sreevidya***Department of Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati***ABSTRACT**

Prolonged fever is a common problem faced by clinicians in everyday practise. Since the first description of the entity “fever of unexplained origin” by Petersdorf and Beeson in 1961, the case definition of this entity was further refined with modifications over the last 55 years. Durack and Street proposed noteworthy changes in the definition of “fever of unknown origin (FUO)”. First, they divided FUO into four groups, namely, classic, nosocomial, human immunodeficiency virus (HIV) related and neutropenic FUO. They also proposed a change in the time frame from “one week hospital study” to “three outpatient visits or three days of in-hospital investigations”. The more recent definition modified the temperature recording of above 38.3 °C (101 °F) on “several occasions” to “at least two occasions” and has listed the minimum essential laboratory testing required for diagnosis. The last five decades have also witnessed a change in the aetiological spectrum of FUO. Infectious diseases like tuberculosis are still common causes of FUO in India; an increase in non-infectious causes of FUO are increasingly being documented in studies from the west. In spite of great advances in imaging and laboratory diagnostic methods a significant number of patients with FUO remained undiagnosed. Studies from other parts of the world have shown 9%-78% cases of FUO to remain undiagnosed while studies from India have shown this figure to be 0%-27.4%. Generating reliable epidemiological data regarding the aetiological spectrum of FUO will facilitate development of optimal work-up strategy to establish the aetiological diagnosis and facilitate the specific tests.

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INTRODUCTION

Prolonged fevers always stood as a challenge for physicians in diagnosing and treating them since time immemorial. The term fever of unknown origin (FUO) is used for those prolonged fevers where history, thorough clinical examination, investigations couldn't help in diagnosing the cause of fever. Going back to year 1930, studying the aetiological causes of fever of unknown origin was first attempted by Alt et al¹. All those cases with unresolved fever and without a proper single diagnosis at the time of discharge were included in the study. In 1961, Petersdorf and Beeson² postulated certain criteria in defining FUO. This definition was used for more than three

decades till Durack and Street³ proposed a revised system for classification of FUO, that is more accountable for endemic and emerging diseases, improved diagnostic technologies, and adverse reactions to new therapeutic interventions.

CASE DEFINITION

In 1961 Petersdorf and Beeson published a report on 100 cases of fever of unexplained origin and they gave the first case definition for fever of unexplained origin (Table 1).² They used three criteria in defining this entity. To exclude all the self-limiting acute febrile illnesses they used three weeks criteria and a temperature above 38.3 °C (101 °F) on several

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Table 1: Definitions used for defining “fever of unknown origin”

Petersdorf and Beeson (1961)²	Durack and Street (1991)³	Mulders-Manders et al (2015)⁴
Fever of unexplained origin is diagnosed by presence of <i>all</i> of the following	Classified FOU into four categories	FUO is defined by presence of <i>all</i> of the following
i. Fever >38.3 °C (>101°F) on several occasions	i. Classical FOU	i. Fever >38.3 °C (101 °F) on at least <i>two</i> occasions
ii. Duration of fever > 3 weeks	ii. Nosocomial FOU	ii. Illness duration ≥3 weeks
iii. No certain diagnosis despite 1 week of inpatient investigations	iii. Neutropenic FOU	iii. Diagnosis that remains uncertain after a thorough history taking, physical examination, and the following obligatory investigations; determination of ESR, CRP level; platelet count, leucocyte count total and differential; measurement of haemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibodies and rheumatoid factor; protein electrophoresis; urinalysis; blood cultures (n=3); urine culture; chest x-ray; abdominal ultrasonography and tuberculin skin test
	iv. HIV-associated FOU	
	Classical FOU is diagnosed by presence of <i>all</i> of the following	
	i. Fever >38.3°C (>101°F) on several occasions	
	ii. Duration of fever >3 weeks	
	iii. Failure to reach a diagnosis despite three outpatient visits or three days in the hospital without elucidation of a cause or one week of “intelligent and invasive” ambulatory investigation	

ESR = erythrocyte sedimentation rate; CRP = C- reactive protein; FOU = fever of unknown origin

occasions to exclude the cases of habitual hyperthermia. Third criteria included in the definition is uncertainty in the diagnosis after one week of hospital study. They have selected this time interval as it would take that much time for the usual haematological, serological and radiological reports to arrive.

In 1991 Durack and Street³ modified the definition given by Petersdorf and Beeson² and referred this entity as fever of unknown origin

(FUO). They made two noteworthy changes that included dividing FUO into four groups namely classic, nosocomial, human immunodeficiency virus (HIV) related and neutropenic FUO. This division is rationale as the classical FUO differs from the rest of the three entities both in the spectrum of underlying disease and the clinical approach. The definition for classic FUO given by them (Table 1) is broader and is closely related to the earlier definition of FUO. The second modification is with regard to the

change in time frame from one week's hospital study to three outpatient visits or three days of in-hospital investigations.

The earlier definitions by Petersdorf and Beeson², Durack and Street³ (Table 1) had stipulated variable time periods, such as "one week hospital study"², "three outpatient visits or three days of in-hospital stay"³ for the investigations to be carried out. A new definition of FUO (Table 1) has been proposed recently⁴ in which the following modifications were proposed. The term "a temperature recording of above 38.3 °C (101 °F) on "several occasions" has been modified to "at least two occasions"; and instead of stipulating an arbitrary time-period for diagnostic work-up, a set of obligatory investigations⁵⁻⁷ were included in the definition.

EPIDEMIOLOGY

Search strategy

We carried out an online MEDLINE search using the medical subject heading (MeSH) terms "fever of unknown origin", "aetiology", "epidemiology", "India".

Global scenario

With the recent advances in diagnostic aids, true FUO is becoming uncommon. This was supported by a report published in Netherlands⁷, where only 73 cases of FUO were registered between December 2003 and July 2005 at 950 bed academic referral hospital and 2800 bed community hospitals^{1,8}. In a geographical area, it is important to know the causes of FUO, its magnitude and pattern, as it is important for early diagnosis, and management. Some studies were conducted from the year 1913-2010 across the world at different countries. Most of them showed infectious diseases to be the underlying cause in which diagnosis has been made after invasive investigation. The results of those studies and the location, number of subjects included in those studies is shown in (Table 2).^{1,4-20}

Indian scenario

Epidemiological trends in the aetiology of FUO are different in developing countries when compared to that in developed countries. Sparse data are available from India regarding the clinical course and outcome (Table 3).⁹⁻¹⁴

Studies from India revealed that infectious diseases were the leading cause of FUO, followed by malignancies (Table 3). However, among infectious diseases, tuberculosis comprised the major group in two studies^{9,11} done at tertiary care teaching hospitals in east India and one study done at north India¹⁰. Brucellosis and enteric fever were found to be the most common among infectious diseases group in studies done at tertiary care teaching hospital, Srinagar, Kashmir¹³ and at a teaching hospital in central India.¹²

CHANGING TRENDS IN THE AETIOLOGY

In the year 1930 a study on fever of unknown origin was published.¹ Irrespective of the duration of fever all those patients admitted at Peter Bent Brigham hospital, Boston where a single diagnosis could not be arrived after clinical examination and bacteriological examination and in which fever did not resolve at the time of discharge were included in this study¹. Each such case was seen by at least two physicians before categorizing the case into "fever of unknown origin". It showed that in only 11% of cases, infections were found to be the aetiological cause and about 78% of cases remained undiagnosed. This could probably be explained by the unavailability of diagnostic aid at that period.

Since the time of the classic paper by Petersdorf and Beeson,² several studies^{2,5,8,15} that were carried out showed infections to be the major cause of FUO ranging from 20% to 80% and among non-infectious causes inflammatory diseases stood second ranging from 1% to 31% followed by malignancies ranging from 8% to 13%.

Table 2: Comparison of some of the studies on fever of unknown origin from other parts of the world

Study	Year of publication	Period of study	Population studied	Place of study	Study design	No. of cases	Aetiological cause (%)				
							Infections	Neoplasms	Inflammatory diseases	Miscellaneous	No diagnosis
Petersdorf ²	1961	1952-59	Adults	Seattle	P	100	36	19	17	21	7
Knockaert ⁸	1994	1980-89	Elderly	Belgium	ND	47	25	12	31	20	12
Miller ¹⁵	1996	1989-93	AIDS	London	R	79	80	8	1	2	9
De Kleijn ⁵	1997	1992-94	Adults	Netherlands	P	167	26	13	24	7	30
Vanderschueren ¹⁶	2003	1990-99	Adults	Belgium	P	290	20	10	24	13	34
Tabak ¹⁸	2003	1984-01	Adults	Turkey	R	117	34	19	29	4	14
Saltoglu ¹⁷	2004	1994-02	Adults	Turkey	P	87	59	14	18	2	7
Ergonul ¹⁹	2005	1993-99	Adults	Turkey	P	80	52	18	16	3	11
Chin ²⁰	2006	2001-02	Adults	Taiwan	P	94	57	9	7	9	18
Zenone ²¹	2006	1999-05	Adults	France	P	144	23	10	26	15	26
Bleeker-Rovers ⁷	2007	2003-05	Adults	Netherlands	P	73	16	7	22	4	51
Colpan ²²	2007	2001-04	Adults	Turkey	P	71	45	14	27	6	9
Mansueto ²³	2008	1991-02	Adults	Italy	R	91	32	14	12	10	32
Hu ²⁴	2008	2002-03	Adults	China	R	142	36	13	32	05	14
Kucukardali ²⁵	2008	2003-04	Adults	Turkey	P	154	34	14	31	05	16
Efstathiou ²⁶	2010	2001-07	Adults	Greece	P	112	30	11	33	05	21
Ali-Eldin ²⁷	2011	2009-10	Adults	Egypt	P	93	42	30	15	0	12
Naito ²⁸	2013	2011	Adults	Japan	R	121	23.1	10.7	30.6	12.4	23.1

P = prospective; R = retrospective; ND = not described; AIDS = acquired immunodeficiency syndrome

Table 3: Comparison of some of the published studies on fever of unknown origin from India

Study	Year of publication	Period of study	Place of study	Population studied	Study design	No. of cases	Aetiological cause (%)				
							Infections	Neoplasms	Inflammatory diseases	Miscellaneous	No diagnosis
Jung ¹²	1999	1993	Wardha	Adults	P	233	46.4	9	20.1	0.5	24
Handa ¹⁰	1996	1996	New Delhi	Adults	P	121	43.8	8.2	15.7	13.3	19
Kejariwal ¹¹	2001	1998-01	Kolkata	Adults	P	100	53	17	11	05	14
Bandyopadhyay ⁹	2011	2008-09	Kolkata	Adults	P	164	54.8	22	7.4	3.6	12.2
Shantaram ¹⁴	2013	ND	Hyderabad	Adults	ND	100	60	10	24	6	0
Mir ¹³	2014	2010-12	Srinagar	Adults	P	91	43.9	12.1	12.1	4.5	27.4

P = prospective; R = retrospective

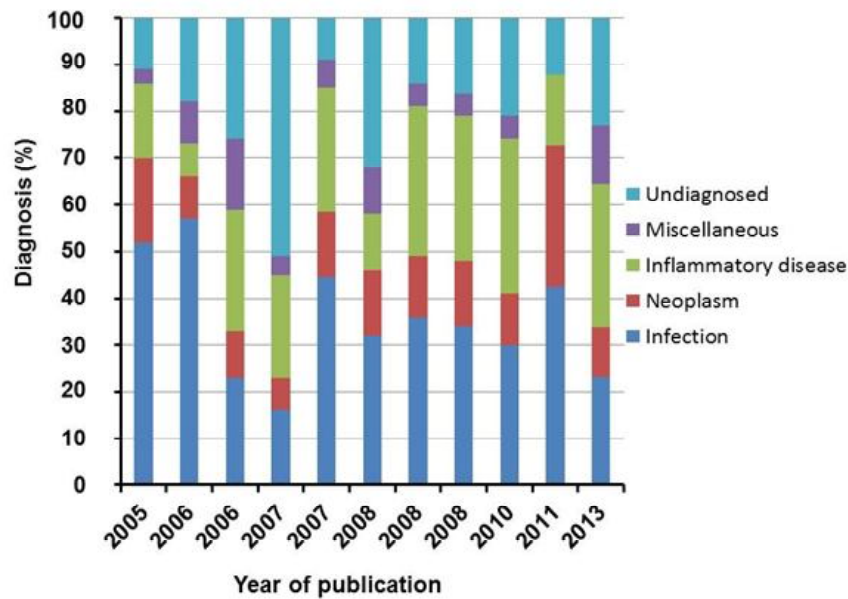


Figure 1A: showing Distribution of aetiological causes of FOU from some of the published studies from other parts of world published since 2005; FOU = fever of unknown origin
 Source: references 7,19-28

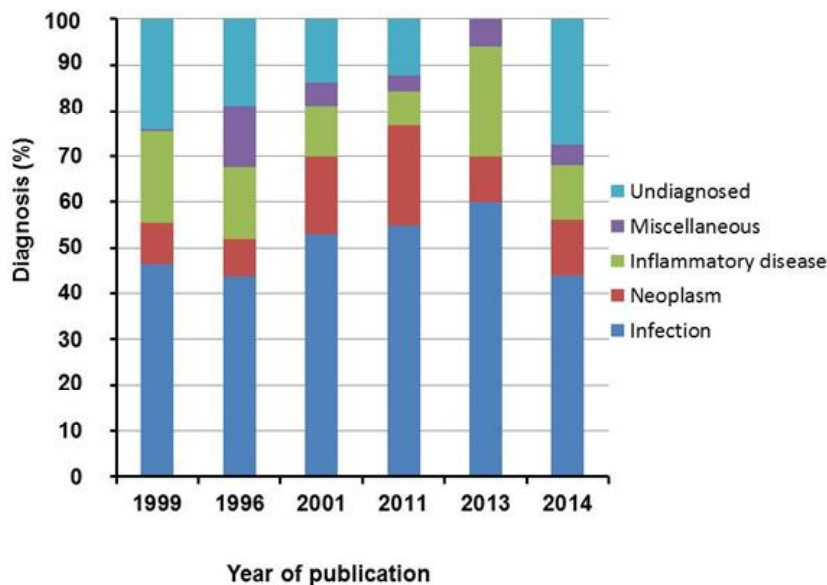


Figure 1B: Distribution of aetiological causes of FOU from some of the published studies from India
 FOU = fever of unknown origin
 Source: references 9-14

In earlier studies aetiological causes of FOU included fewer cases with connective tissue disease. As of now more cases of connective tissue disease (CTD) are being diagnosed due to increased awareness regarding these cases and their numbers as causes of PUO are declining. Extra-pulmonary tuberculosis (EPTB), solid tumours, and abdominal

abscesses are emerging as less frequent causes of FOU presently in developed countries due to early localization of these lesions by radiographic imaging. Image guided biopsies help in diagnosis. Infective endocarditis, which used to be a frequent cause of FOU, has become less common with improved techniques for the isolation of organisms.

From the year 2000-2010^{7,16-26} there has been a decrease in the incidence of infections ranging from 16%-57%, this is in parallel to slight increase in the proportion of cases diagnosed to have inflammatory diseases. This change could be both due to the increasing awareness on inflammatory diseases as well as advances in nuclear scans helping in localising the active focus responsible for fever.

Only few studies⁹⁻¹⁴ were conducted in India to comment on the time trends in aetiological causes of FUO. Available data between the period 1999-2014 showed infectious diseases were the leading cause of FUO ranging from 43.8% to 60%, followed by malignancies ranging from 9% to 22% and inflammatory disease ranging from 7.4% to 24%. The results were similar to the results obtained in other parts of the world during that period. This shows the equal distribution of the disease load across the globe.

In spite of the spectacular advances in imaging and laboratory diagnostic methods, even today, a substantial number of patients with FUO remain undiagnosed (Tables 2 and 3; Figures 1A and 1 B). In studies from India (Table 3) 0%-27.4% of patients remained undiagnosed, while in the studies from other parts of the world, this figure ranged from 9%-78%. Whether these variations merely reflect the changes in the range and availability of diagnostic investigations over time and variations in the diagnostic protocol followed at different centres or, reflect hitherto unknown causes for FUO needs further study. This calls for the need for further research in this area.

Data regarding the commonly encountered aetiological causes of FUO in a given clinical setting and their changing trends will facilitate a focussed diagnostic work-up and an optimal strategy to arrive at the aetiological diagnosis so that appropriate specific treatment can be instituted.

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