

***Changing Face of Fever of Unknown  
Origin (FUO): A Single Hospital  
Study***

*Thesis*

Submitted for partial fulfillment of Master Degree in  
Tropical Medicine

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## *Acknowledgment*

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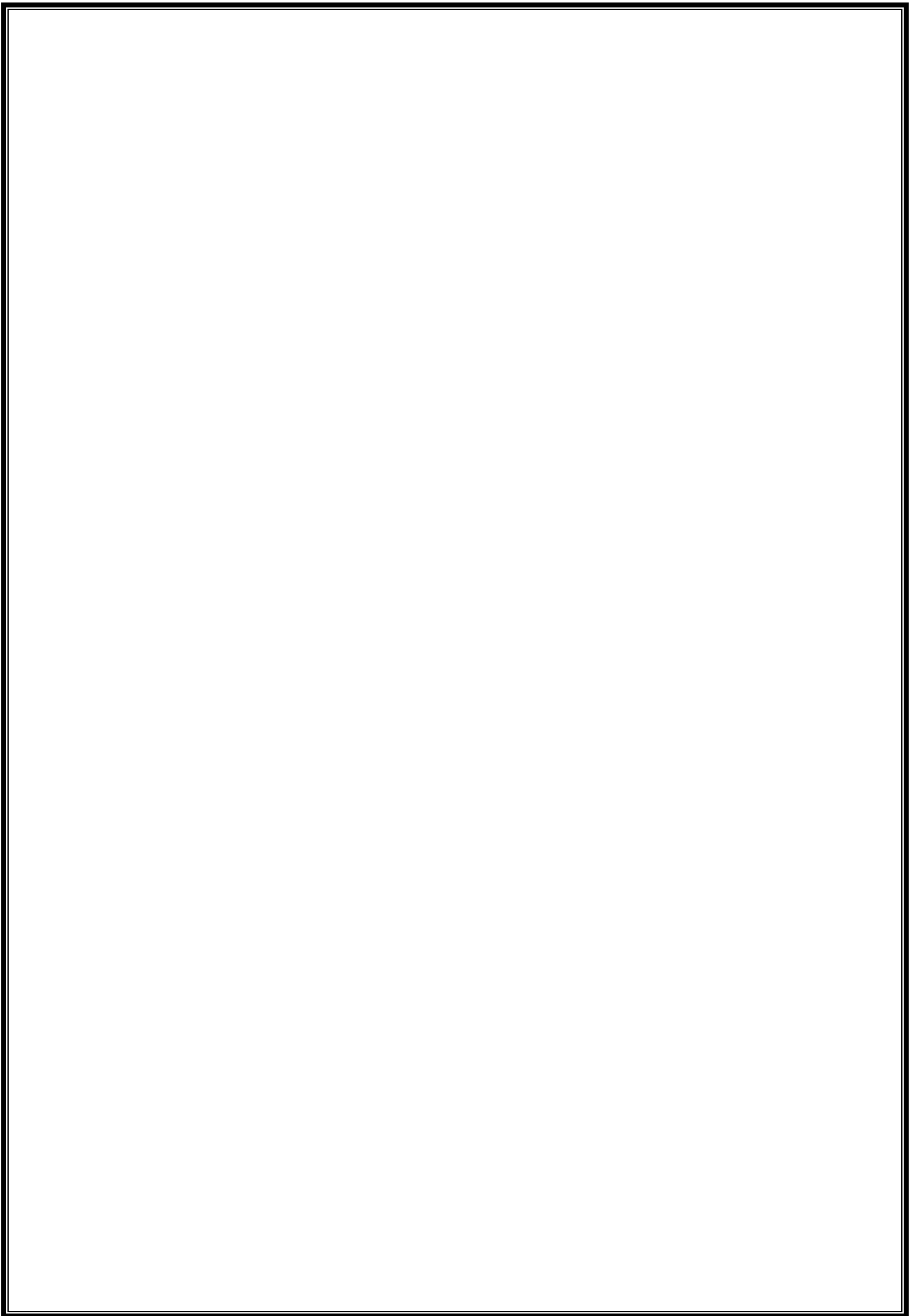
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## LIST OF ABBREVIATIONS

<b>4-MTA</b>	4-Methylthioamphetamine
<b>ACPAs</b>	Anti-citrullinated protein antibodies
<b>ACR</b>	American college of rheumatology
<b>AFB cultures</b>	Acid-Fast Bacilli
<b>AIDS</b>	Acquired immunodeficiency syndrome
<b>ANA</b>	Anti-nuclear antibody
<b>ANCA</b>	Anti-neutrophil cytoplasmic antibody
<b>anti-CCP</b>	Cyclic citrullinated peptide
<b>anti-ENA</b>	Extractable nuclear antigen
<b>ASO</b>	Antistreptolysin O
<b>BCG</b>	Bacillus Calmette–Guérin
<b>CD4</b>	cluster of differentiation 4
<b>CDC</b>	Centers for disease control and prevention
<b>CMV</b>	Cytomegalovirus
<b>CNS</b>	Central nervous system
<b>CRP</b>	C-reactive protein
<b>CSD</b>	Cat scratch disease
<b>CSF</b>	Cerebro spinal fluid
<b>CT</b>	Computer tomography
<b>DNA</b>	Deoxyribonucleic acid
<b>EBNA</b>	Epstein-Barr nuclear antigen

<b>EBV</b>	Epstein-Barr virus
<b>ELISA</b>	Enzyme linked immunosorbent assay
<b>ESR</b>	Erythrocyte sedimentation rate
<b>FBT</b>	Fecal bacteriotherapy
<b>FDA</b>	US Food and Drug Administration
<b>FMF</b>	Familial Mediterranean fever
<b>FUO</b>	Fever of unknown origin
<b>HAART</b>	Highly Active Antiretroviral Therapy
<b>HCQ</b>	Hydroxychloroquine
<b>HHV-6</b>	Human herpesvirus 6
<b>HIV</b>	Human immunodeficiency virus
<b>IAAT</b>	Immunosorbent agglutination assay test
<b>IBD</b>	Inflammatory bowel disease
<b>IFA</b>	Indirect fluorescent antibody assay
<b>IL</b>	Interleukin
<b>IM</b>	Intramuscular
<b>IV</b>	Intravenous
<b>IVIGs</b>	Intravenous immunoglobulins
<b>LAT</b>	Latex agglutination test
<b>MDMA</b>	3,4-methylenedioxy-N-methylamphetamine
<b>MDR</b>	Multi drug resistant
<b>MEFV</b>	Mediterranean fever
<b>MPT</b>	Metaraminol Provocative Test
<b>MRI</b>	Magnetic resonance imaging

<b>NSAIDs</b>	Non-steroidal anti-inflammatory drugs
<b>PCR</b>	Polymerase chain reaction
<b>PMA</b>	para-Methoxyamphetamine
<b>PMR</b>	Polymyalgia rheumatica
<b>RA</b>	Rheumatoid arthritis
<b>RF</b>	Rheumatoid factor
<b>SLE</b>	Systemic Lupus Erythematosus
<b>SPEP</b>	Serum Protein Electrophoresis
<b>TB</b>	Tuberculosis
<b>UC</b>	Ulcerative colitis
<b>VCA</b>	Viral capsid antigen
<b>VDRL</b>	Venereal Disease Research Laboratory
<b>XDR</b>	Extensively drug resistant



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## **Introduction**

One of the problems most frequently encountered in medical practice is the diagnosis of prolonged fever, with or without local signs of disease. This problem confuses both the physician and the patient.

Unlike the 1910's when most cases of FUO were restricted to a few infectious diseases, the differential diagnosis for FUO today comprises over 200 disorders and is among the longest of any condition in medicine. Fortunately, a meticulous history, a thorough physical examination, the use of investigative procedures, and constant reassessment of the evidence will usually reveal the cause of the patient's fever. A valuable measure is to know how to apply available diagnostic tools appropriately and knowing when careful patient observation is better than further investigative or therapeutic intervention. **(Dykewicz, 2003).**

Most febrile conditions are readily diagnosed on the basis of presenting symptoms and a problem-focused physical examination. Occasionally, simple testing such as a complete blood count or urine culture is required to make a definitive diagnosis. Viral illnesses (e.g., upper respiratory infections) account for most of these self-limiting cases and usually resolve within two weeks. **(Dykewicz, 2003).**

Fevers of unknown origin (FUO) were first described in 1961 by Petersdorf and Beeson, when the pair outlined 100 patients that presented with FUO. Their research is best remembered for establishing the three criteria that define FUO. First, a minimum measured temperature of 38.3°C was required. Secondly, the febrile states should occur on several occasions over a period of at least three weeks. Finally, a minimum of one week of investigations was required to allow adequate time for test results to return. **(Petersdorf and Beeson, 1961).**

The modern definition of FUO is based on modifications around these criteria. These adaptations take into account four specific patient subtypes: classic, nosocomial, immune deficient (neutropenic), and HIV-associated. In addition to

having a documented fever of 38.3°C, each category has a different set of criteria and list of likely causes.

1. **Classic FUO** - When temperature > 38°C (>101°F) recorded on several occasions occurring for more than three weeks in spite of investigations on three outpatient visits or three days of stay in hospital or one week of invasive ambulatory investigations is called classic FUO.
2. **Nosocomial FUO** - When temperature more than >38.3°C(> 101°F) is recorded on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest or incubating on admission is called nosocomial FUO. Three days of investigations including at least two days incubation of cultures, is the minimum requirement for this diagnosis.
3. **Neutropenic FUO** - When temperature of > 38.3°C (>101°F) on several occasion is observed in a patient whose neutrophil count is less than 500/microliter or is expected to fall to that level in 1 or 2 days is called neutropenic FUO. This diagnosis should be considered when investigation including at least two days of incubation of cultures. It is also called immunodeficient FUO.
4. **HIV associated FUO** - When temperature of > 38.3°C (>101°F) on several occasions is found over a period of more than 4 weeks for our patient or more than three days for hospitalized patients with HIV infection is called HIV associated FUO. This diagnosis is considered if appropriate investigations over three days including two day of incubation of cultures reveals no source.(**Durack and Street, 1991**)

The differential diagnosis for FUO can be divided into four suggested classes: infection, malignancy, collagen vascular disease, and miscellaneous.(**ArnowardFlaherty, 1997**).

The following table outlines the proportion each class contributes, and provides the most common etiologies within each.