

**Review Article****A Clinical Approach to a Case of Fever of Unknown Origin**

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Introduction

Fever of unknown origin (FUO) is an intellectual and diagnostic challenge. Radically different approach is required in developing countries like India due to limited access to diagnostic facilities. Fever of unknown origin was first described by Petersdorf and Beeson¹ in 1961, when study was conducted in 100 patients presenting with FUO. They established 3 criteria to define FUO² –

- Minimum measured temperature of 38.3° C (101 ° F) on several occasions.
- Fever over a period of at least 3 weeks.
- Diagnosis could not be reached after 3 outpatient visits or 3 days of hospitalization.

Newer Classification by Durack and Street

Newer classification of FUO has been proposed by Durack and Street, taking into account 4 specific patient subtypes –

- Classic FUO
- Nosocomial FUO
- Neutropenic FUO (<500/mm³)
- FUO associated with HIV infection

Table 1: Categories of FUO^{3,4}

Category	Criteria
1.Classical	<ul style="list-style-type: none"> Duration of minimum 3 weeks, Evaluation of minimum 3 outpatient visits or 3 days of hospitalization.
2.Nosocomial	<ul style="list-style-type: none"> Hospitalization for min. 24 hours Do not have fever and not in incubation period on admission Evaluation of at least 3 days
3.Neutropenic	<ul style="list-style-type: none"> Neutropenia (ANC <500/mm³). Evaluation of atleast 3 days in hospital.
4.HIV associated	<ul style="list-style-type: none"> Duration of minimum 4 weeks as outpatient or 3 days as inpatient. Diagnosed case of HIV.

Common causes of FUO

Classic FUO	Nosocomial FUO
Tuberculosis Abscesses Bacterial endocarditis Non-hodgkins lymphoma Acute leukemia Systemic lupus erythromatosis Takayasu's arteritis Factitious fever	post-operative abscesses, haematoma foreign bodies infected cannula, catheters clostridium defficile colitis acalculous cholecystitis deep vein thrombosis pulmonary embolism drug fever
In classis FUO among all cases infectious causes are responsible in 53% cases, neoplasms in 17%, granulomatous disease in 14%, collagen disorders in 11% pulmonary embolism, drug fever and factitious fever in 5% of cases	In this category majority of cases are due to infectious etiology and only smaller percentage of cases are due to noninfectious causes like pancreatitis, pulmonary embolism, deep vein thrombosis, acalculous cholecystitis and drug fever

In majority of the cases fever is associated with self limiting infection (mostly viral)

Neutropenic fever

In patients with neutropenia 60% of FUO are infectious in origin and out of which about 20% are bacteremic like E.coli, klibsiella species, Pseudomonas, staph. Herpes simplex and other viral infections are also common. These patients are also more prone for fungal infections specially oral thrush and esophageal candidiasis.

HIV associated fever

In HIV patients 90% of the cases are infectious and 10% are due to lymphoma or due to drugs. Common infections causing fever in these patients are tuberculosis, pneumonia, abscesses (liver, renal, perinephric) splenic abscesses Cryptococcus, histoplasmosis, candidiasis, pneumocystis jervei. Immune reconstitution inflammatory syndrome after starting the antiretroviral drugs can also present with fever. HIV virus infection itself can cause fever when no other infection is present.

Pathogenesis

- Fever is caused by exogenous pyrogens like lipopolysaccharide toxins, and endogenous pyrogen like interleukin1, tumor necrosis factor (TNF). Prostaglandin E raises the CNS set point and in peripheral tissues causes myalgias and arthralgias.
- Hypothalamic set point increases and hence raise the body thermostat levels
- Peripheral vasoconstriction occurs and patient feels cold
- Shivering occurs to raise the body temperature to a new set point
- Peripheral vasodilation occurs and leads to sweating when set point is lowered by the antipyretic drug

Diagnostic approach to fever of unknown origin

- Good clinician is the one who makes least mistakes in diagnosis of common

condition, not one who makes occasional brilliant guesses

- Meticulous detailed clinical history is essential
- Attention must be paid to chronology of symptoms
- History must include relation of symptoms to medications, pet exposure, sick contacts, travel, trauma, prosthetic implants, occupation, immunization and immune status.
- In cases of rashes: site of onset, direction and rate of spread, type of rashes and relation with fever
- History of preexisting diseases like COPD , cardiac disease, diabetes
- History of IV drug abuser hospitalization, HIV or alcohol intake must be taken.
- History of presence of foreign bodies like tampon, nasal packages, barrier contraceptive and exposure to bioterrorism
- History of burning micturition in past or increased frequency of micturition in elderly.

Associated symptoms and etiology to be suspected

Headache	Sinusitis, temporal arteritis, trigeminal neuralgia, ICSOL, meningitis
Conjunctival suffusion	Leptospirosis
Orbital pain	Glaucoma, orbital cellulitis
Neck pain	Thyroiditis, temporal arteritis, epidural abscess, tubercular lymphadenitis
Throat pain	Tonsillitis, retropharyngeal abscess, peritonsillar abscess
Chest pain	Infective endocarditis, pericarditis, pleuritis
Abdominal pain	Appendicitis, chronic cholecystitis, reactive lymphadenopathy
Joint involvement	Rheumatic, rheumatoid, tubercular or bacterial arthritis. Post viral syndrome

Physical finding and the suspected etiology

In a study from India¹⁴, infections were the commonest cause, being responsible for 53% of

cases of FUO and Tuberculosis was most common infection. After infections, neoplasm was next most common cause (17 %) followed by collagen vascular disease (11 %), miscellaneous were responsible in 5% cases and in 14% cause of fever remained undiagnosed. On contrary to popular beliefs, we want to emphasize that enteric fever cannot persist for more than 3 to 4 weeks. So, for any fever lasting for more than 1 month, enteric (typhoid) fever should be excluded.

Clinical Approach

History- One fourth of patients who say they have been febrile for 6 months or longer actually have no true fever or underlying disease. Instead, the usual normal circadian variation in temperature (temperature is 0.5 to 1 ° C higher in the afternoon than in the morning) is interpreted as abnormal.

Physical Examination

As fever may result from involvement of any of the body’s systems,a thorough physical examination is warranted.

Table no. 3⁸ is showing significance of subtle physical findings in a patient of FUO.

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
Head	Sinus tenderness	Sinusitis
Back of Neck	Tenderness	Epidural abscess
Front of neck	Tenderness	Thyroiditis
Temporal artery	Nodules	Temporal arteritis
Oropharynx	Tender tooth	Periapical abscess
Fundi or conjunctiva	Choroid tubercle , roth’s spot	disseminated granulomatosis ,endocarditis
Lymphadenopathy	Enlargement ,tenderness	Tuberculosis ,neoplasm
Heart	Murmur	Infective endocarditis
Liver	Liver enlargement	Liver abscess, subdiaphragmatic abscess, chronic malaria
Spleen	Splenomegaly	Malaria, kala azar, tropical splenomegaly, lymphoma, granulomatous disorders
Rectum	Perirectal	Abscess

	fluctuance, tenderness; Prostatic tenderness	
Lower extremities	Calf tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, splinter haemorrhages, subcutaneous nodules ,clubbing	Vasculitis, endocarditis
Tonsils	Enlargement	Tonsillitis
Heart sounds	Murmur, pericardial rub	Infective endocarditis, pericarditis
Chest auscultation	Occasional ronchi or crepts	Deep seated parenchymal disease

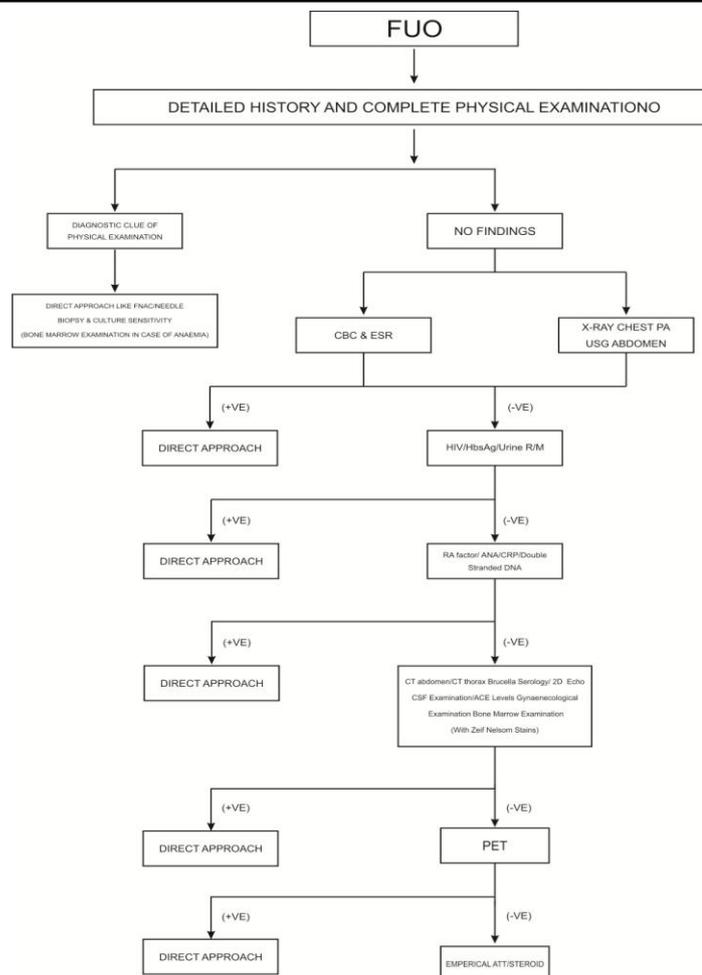
Laboratory Workup of FUO

If we get clues from history and physical examination, then investigations should be tailored accordingly.

When history or physical examination is not suggestive, then clinician should start with basic set of investigations to proceed further. Although there is no uniform set of investigations but the basic group should include complete blood counts, erythrocyte sedimentation rates , liver function test, urinalysis ,three blood cultures, rheumatological markers (ANA, RA Factor, ANCA), HIV antibody.^{3,7}

All patients with a PUO should have a chest radiograph.

Instead of going for a battery of investigations a radical approach is to be used to minimize



Management of FUO

Emphasis should be given to obtain a diagnosis

Antipyretic therapy should be given on regular schedule rather than intermittently. However withholding the antipyretics will also help in observation of fever, its grade and pattern Paracetamol is the preferred antipyretic and may be given in 100 ml infusion in cases of vomiting, gastritis or high grade fever.

As many as 30% of patients remain undiagnosed at the time of discharge, despite a meticulous work up.¹³ In a study of 199 cases of FUO, 61 patients (30%) were discharged without a casual diagnosis but at the end of 5-year follow up, only 2 of the 61 patients had died secondary to the FUO,¹³ pointing to the generally favorable prognosis of untreated FUO.¹³

Empirical therapy

Empirical therapy is a last resort, given the good prognosis of most patients with FUO persisting

without a diagnosis. If even after extensive work up cause of fever is not ruled out antitubercular therapy or steroids must be used after correlating the symptoms and history of the patient.¹⁴

Summary

The challenge that physicians face against FUO still lingers. The best way to tackle it is by a thorough history, meticulous physical examination catching all the seemingly insignificant hints and proceeding to appropriate laboratory investigations. The initial tests should focus on ruling out the basic etiologies i.e. infection, inflammation and malignancy, after which, further proceedings may be undertaken. But despite all this, up to 30%¹³ cases may remain unsolved at the time of discharge, prompting further interest and studies in this ever enigmatic field.

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