Chapter 11
Approach to the Patient with Fever of Unknown Origin

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INTRODUCTION
Fever of unknown origin (FUO) in adults is defined as a temperature higher than 38.3°C (100.9°F) that lasts for more than 3 weeks with no obvious source despite appropriate investigation. The four categories of potential etiology of FUO are classic, nosocomial, immune deficient and human immunodeficiency virus (HIV)-related. The four subgroups of the differential diagnosis of FUO are infections, malignancies, autoimmune diseases and miscellaneous. A thorough history, physical examination and standard laboratory testing remain the basis of the initial evaluation of the patient with FUO. Newer diagnostic modalities including updated serology, viral cultures computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan have important role in the assessment of these patients with FUO.

DEFINITION AND CLASSIFICATION
Fever of unknown origin remain one of the most common and difficult diagnostic problems faced daily by clinicians. Petersdorf and Beeson first coined the term “fever of unknown origin” in 1961 and explicitly defined as temperature more than 38.3°C (101°F), duration of fever more than 3 weeks and failure to reach to diagnosis despite 1 week of inpatient investigation.

In 1991 DT Durrack and AC street suggested few changes to the earlier definition and proposed four following types of FUO:

1. **Classic FUO**: When temperature is more than or equal to 38.3°C (101°F) recorded on several occasions occurring more than 3 weeks undiagnosed in spite of investigations on 3 OPD visits or 3 days of stay in hospital or 1 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 manifested or incubating on admission is called nosocomial FUO. Three days of investigations including at least 2 days incubation of cultures is the minimum requirement for this diagnosis.

3. **Neutropenic FUO (immune deficient FUO)**: This is defined as a temperature of more than or equal to 38.3°C (101°F) on several occasions in a patient whose neutrophil count is less than 500/µL or is expected to fall to that level in 1-2 days, and a specific cause is not identified after 3 days of investigations including at least 2 days of incubation of cultures.

4. **Human immunodeficiency virus associated FUO**: This is defined as temperature more than or equal to 38.3°C or (≥101°F) on several occasions over a period of 4 weeks for outpatients or more than 3 days for hospitalized patients with HIV infection when appropriate investigations for 3 days, including 2 days incubation of cultures reveal no source.

PREVALENCE AND CAUSES OF FEVER OF UNKNOWN ORIGIN
The prevalence of FUO among adult hospitalized patients is reported to be 2.9%. The spectrum of FUO etiology may include more than 200 diseases. According to studies conducted to date, the diseases taking part in FUO etiology and their rates are as follows: infections (21–54%), noninfectious inflammatory causes (13–24%), neoplasms (6–31%) and other causes (4–6%). The incidence of various causes differ with geographical, age and sex difference and development level of countries and the experience of clinicians.

Indian Scenario (Table 2)
Infectious diseases notably tuberculosis has been the most important cause of FUO in our country in all the studies published. Among noninfectious causes autoimmune disorders and neoplasm are fast becoming important differential diagnosis.

NIZAM INSTITUTE OF MEDICAL SCIENCES (NIMS) EXPERIENCE
Hundred cases of classic FUO were evaluated in 10 years, 64 were males and 36 were females. The age range was from 18–70 years with peak incidence is 30–40 years. Etiological basis was as follows, infection 60 cases, collagen vascular disease 24, neoplasms 10 and miscellaneous 6. Further break-up of each group was as follows, infection: TB 45, nontuberculosis 15. Among the patients with tuberculosis 10 were disseminated, 12 were lymph nodal, 7 were Pott’s disease, 5 were intestinal, 4 were renal and 7 were pericardial. Among nontubercular etiology 3 were brucellosis, 2 ricketsial, 5 protozoa (falciparum malaria), infective endocarditis 2, fungal 2, viral 1 (CMV). Out of 24 collagen vascular diseases SLE 14, adult stills disease 4, polymyalgia rheumatica 2, MCTD 2, and poly arteritis nodosa 2. Among the neoplasm, lymphoma 8, renal cell carcinoma 2. Among miscellaneous sarcoidosis 2, granulomatous hepatitis 1, LA myxoma 2 and drug fever 1.

Examples of subtle physical findings having specific significance in patients with fever of unknown origin shown in Table 4.
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### TABLE 1 | Summary of classification and major factors of the four subtypes of fever of unknown origin

<table>
<thead>
<tr>
<th></th>
<th>Classic FUO</th>
<th>Nosocomial FUO</th>
<th>Immunodeficient FUO</th>
<th>HIV-related FUO</th>
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<tr>
<td><strong>Definition</strong></td>
<td>&gt;38°C 3 wk, &gt;2 visits or 3d in hospital</td>
<td>&gt;38°C, 3d, not present or incubating on admission</td>
<td>&gt;38°C, 3d, negative cultures after 48 hrs with &lt; 1,000 PMN /μL</td>
<td>&gt;38°C &lt;3w for inpatients, HIV infection confirmed</td>
</tr>
<tr>
<td><strong>Patient location</strong></td>
<td>Community, clinic or hospital</td>
<td>Acute care hospital</td>
<td>Hospital or clinic</td>
<td>Community, clinic or hospital</td>
</tr>
<tr>
<td><strong>Leading causes</strong></td>
<td>Infections, inflammatory conditions, cancer, undiagnosed, habitual hyperthermia</td>
<td>Nosocomial infections, postoperative complications, drug fever</td>
<td>Majority due to infections, but cause documented in only 40–60%</td>
<td>(HIV primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis</td>
</tr>
<tr>
<td><strong>History emphasis</strong></td>
<td>Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder</td>
<td>Operations and procedures, devices, anatomic considerations, drug treatment</td>
<td>Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder</td>
<td>Drugs, exposures, risk factors, travel contacts, stage of infection</td>
</tr>
<tr>
<td><strong>Examination emphasis</strong></td>
<td>Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia rectum or prostate, lower limb deep veins.</td>
<td>Wound, drains, devices, sinuses, urine</td>
<td>Skin folds, IV sites, lungs, perianal area</td>
<td>Mouth, sinuses, skin, lymph nodes, eyes, lungs perianal area</td>
</tr>
<tr>
<td><strong>Investigation emphasis</strong></td>
<td>Imaging, biopsies, sedimentation rate, skin tests</td>
<td>Imaging, bacterial cultures</td>
<td>CXR, bacterial cultures</td>
<td>Blood and lymphocyte count; serologic test: CXR; stool examination; biopsies of lung, bone marrow and liver for cultures and cytological tests, brain imaging</td>
</tr>
</tbody>
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### TABLE 2 | Comparison of three major etiologic categories of fever of unknown origin in various series reported in India

<table>
<thead>
<tr>
<th></th>
<th>Handa et al⁹</th>
<th>D Kejarwal et al¹⁰</th>
<th>Dipanjan Bandypadhyay et al¹²</th>
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<tbody>
<tr>
<td><strong>Infections</strong></td>
<td>43.8%</td>
<td>53%</td>
<td>58.53%</td>
</tr>
<tr>
<td><strong>Collagen vascular disease</strong></td>
<td>15.7%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Neoplasms</strong></td>
<td>8.3%</td>
<td>17%</td>
<td>22</td>
</tr>
</tbody>
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### TABLE 3 | Common etiologies of fever of unknown origin

| **Infections** | Tuberculosis especially extrapulmonary, abdominal abscess, pelvic abscess, dental abscesses, endocarditis, osteomyelitis, sinusitis, prostatitis, viral (cytomegalovirus, Epstein-Barr, HIV) ricketsial, fungal, malaria, typhoid and kala azar |
| **Malignancies** | Lymphoma, chronic leukemia, metastatic cancer, renal cell carcinoma, colon cancer, hepatoma and sarcomas |
| **Autoimmune conditions** | Adult still’s disease, polymyalgia rheumatica, temporal arthritis, SLE, RA, Reiter’s syndrome, vasculitides and inflammatory bowel disease |
| **Miscellaneous** | Drug-induced fever, factitious fever sarcoidosis, granulomatous hepatitis, DVT and PTE |

### DIAGNOSTIC APPROACH AND CLINICAL PERSPECTIVE

Because FUOs are caused by such a wide variety of disorders, the diagnostic approach to the FUO patient is often extensive consisting of three phases:¹³-¹⁵

1. Initial evaluation should include relevant FUO history as well as physical examination that look particularly for diagnostic finding relevant to FUO (Table 3). Initial nonspecific laboratory tests provide clues pointing toward a particular diagnosis while simultaneously eliminating other diagnosis.

2. Second phase of FUO evaluation consists of a focused history and comprehensive physical examination with additional relevant lab tests.
**Infectious Diseases**

**Flow chart 1: Algorithm for the diagnosis of fever of unknown origin**

1. **Complete history and physical examination**
2. **Positive findings → Yes → Order appropriate and specific diagnostic testing**
3. **No**
   - **CBC, ESR, Urine analysis, culture, blood culture, LFT, PPD skin test, chest radiograph, muscle enzyme and abdominal ultrasonogram**
4. **Positive results → Yes → Order appropriate diagnostic test and follow-up**
5. **No**
   - **CT chest abdomen, pelvis with contrast**

**Assign to most likely category**

- **Infection**
  - Urine, sputum culture, AFB, Brucella, HIV, CMV, EBV serology, Lumbar puncture, Temporal artery biopsy, ECHO cardiogram (TEE), Gallium 67 scan, FDG PET scan

- **Malignancies**
  - Hematologic assessment, S protein electrophoresis, Bone marrow aspiration and biopsy, Lymph node biopsy, Colonoscopy, Liver biopsy

- **Autoimmune diseases**
  - ASO, RF, ANA, ANCA, Ferritin, Muscle and skin biopsy

**After full work-up for FUO**

- **If arrived at diagnosis**
  - Specific therapy

- **Empiric therapy**
  - Anti-TB, antimicrobial therapy
  - NSAIDs steroid

- **If no diagnosis**
  - Watchful waiting
3. Third phase of FUO work-up is the definitive diagnostic testing including specific lab tests and biopsy to confirm the diagnosis (Flow chart 1) shows algorithm for FUO work-up.

TREATMENT OF FEVER OF UNKNOWN ORIGIN

The emphasis in patients with classic FUO is on continued observation and examination with avoidance of “Shotgun” empirical therapy. However, vital signs instability or neutropenia is an indication for empirical therapy with fluoroquinolone plus piperacillin. If Mantoux test is strongly positive and granulomatous disease is suggested (and sarcoid seems unlikely) then a therapeutic trial for tuberculosis should be undertaken with treatment continued for up to 6 weeks. A failure of the fever to respond over this period suggests other alternative diagnosis. A response of rheumatic fever and still’s disease to aspirin and NSAIDs may be dramatic. The effects of glucocorticoids on temporal arteritis and polymyalgia rheumatica and granulomatous hepatitis are equally dramatic. The initiation of empirical therapy, doesn’t mark the end of the diagnostic work-up, rather it commits the physician to continued thoughtful reexamination and evaluation. Patience, compassion, equanimity, vigilance and intellectual flexibility are indispensable attributes for the clinician in dealing successfully with FUO.

CONCLUSION

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 perplexes both the physician and the patient and is labeled as FUO. The definition, classification and clinical approach, diagnosis and treatment have been discussed. It is important to realize FUO may represent uncommon manifestation of common disease. Hence the work-up should be cost effective and thoughtful and clinically appropriate. Empirical treatment sometimes may be worse than disease. Hence the work-up should be cost effective and thoughtful and clinically appropriate. The emphasis in patients with classic FUO is on continued observation and examination with avoidance of “Shotgun” empirical therapy. However, vital signs instability or neutropenia is an indication for empirical therapy with fluoroquinolone plus piperacillin. If Mantoux test is strongly positive and granulomatous disease is suggested (and sarcoid seems unlikely) then a therapeutic trial for tuberculosis should be undertaken with treatment continued for up to 6 weeks. A failure of the fever to respond over this period suggests other alternative diagnosis. A response of rheumatic fever and still’s disease to aspirin and NSAIDs may be dramatic. The effects of glucocorticoids on temporal arteritis and polymyalgia rheumatica and granulomatous hepatitis are equally dramatic. The initiation of empirical therapy, doesn’t mark the end of the diagnostic work-up, rather it commits the physician to continued thoughtful reexamination and evaluation. Patience, compassion, equanimity, vigilance and intellectual flexibility are indispensable attributes for the clinician in dealing successfully with FUO.

REFERENCES