Chapter 11

Approach to the Patient with Fever of Unknown Origin

V Shantaram, AMVR Narendra

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[1,2] temperature more than 38.3°C (101°F)[3] duration of fever more than 3 weeks[4] failure to reach to diagnosis despite 1 week of inpatient investigation.[1] In 1991 DT Durrack and AC street suggested few changes to the earlier definition and proposed four following types of FUO[2] (**Table 1**):

Current Types of Fever of Unknown Origin

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%.[4] The spectrum of FUO etiology may include more than 200 diseases.[5] 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 (4–6.5%).[6-8] 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.[9-12] 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 **(Table 3)**.

Examples of subtle physical findings having specific significance in patients with fever of unknown origin shown in **Table 4**.

TABLE 1 | Summary of classification and major factors of the four subtypes of fever of unknown origin

	Classic FUO	Nosocomial FUO	Immunodeficient FUO	HIV-related FUO
Definition	>38°C 3 wk, > 2 visits or 3d in hospital	>38°C, 3d, not present or incubating on admission	>38ºC, 3d, negative cultures after 48 hrs with < 1,000 PMN /µL	>38°C <3w for inpatients, HIV infection confirmed
Patient location	Community, clinic or hospital	Acute care hospital	Hospital or clinic	Community, clinic or hospital
Leading causes	Infections, inflammatory conditions, cancer, undiagnosed, habitual hyperthermia	Nosocomial infections, postoperative complications, drug fever	Majority due to infections, but cause documented in only 40–60%	(HIV primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel contacts, stage of infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia rectum or prostate, lower limb deep veins.	Wound, drains, devices, sinuses, urine	Skin folds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin testes	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic test: CXR; stool examination; biopsies of lung, bone marrow and liver for cultures and cytological tests, brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment	Antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

TABLE 2 | Comparison of three major etiologic categories of fever of unknown origin in various series reported in India

	Handa et al[9]	D Kejarwal et al[10]	Dipanjan Bandyopadhyay et al[12]
Infections	43.8%	53%	58.53%
Collagen vascular disease	15.7%	11%	11%
Neoplasms	8.3%	17%	22

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 arteritis, 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.

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

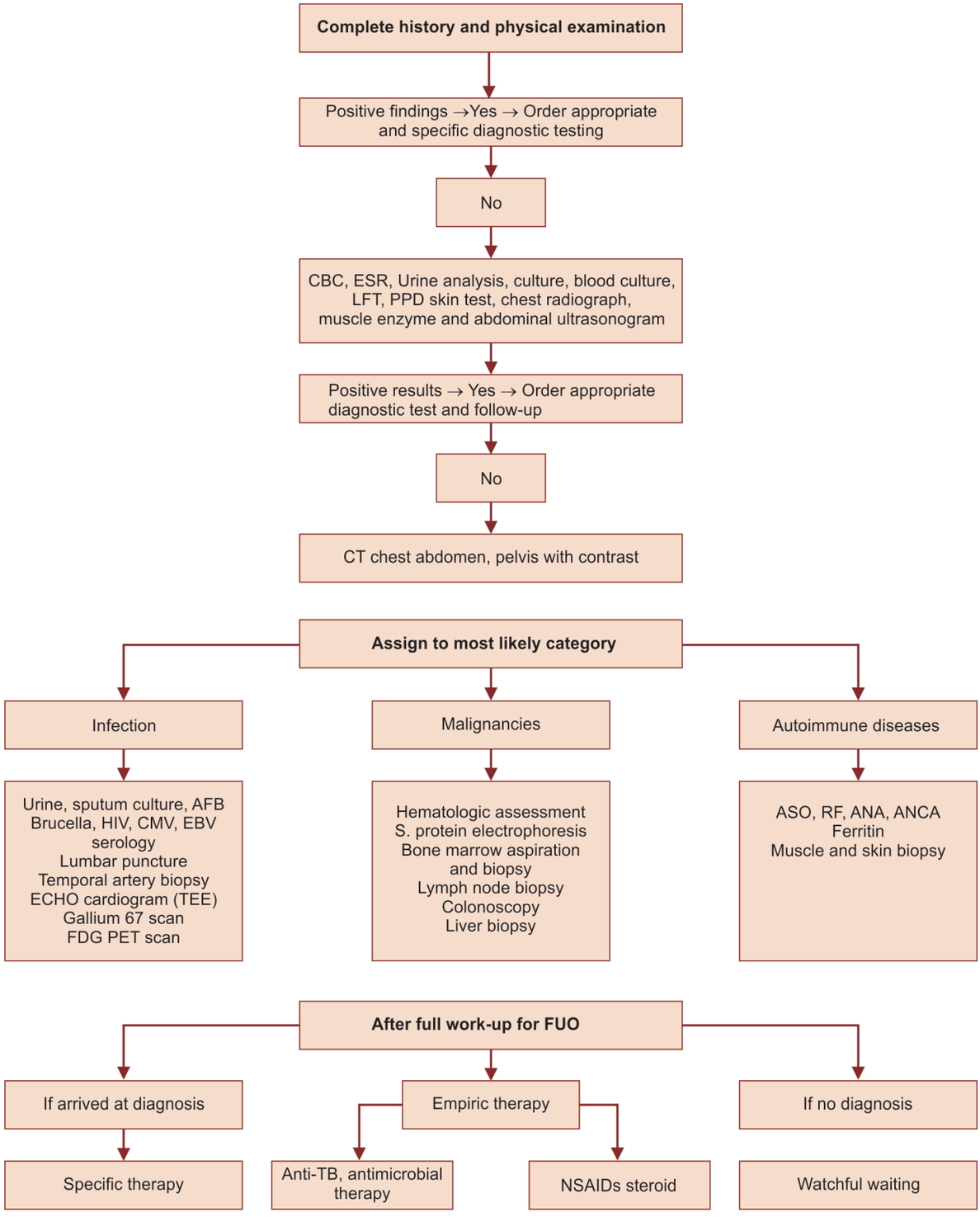

TABLE 4 | Examples of subtle physical findings having specific significance in patients with fever of unknown origin

Body site	Physical finding	Diagnosis
Head	*Sinus tenderness*	*Sinusitis*
Temporal artery	Nodules, reduced pulsation	Temporal arteritis
Oropharynx	Ulceration, tender tooth	Disseminated histoplasmosis, periapical abscess
Fundi or conjunctiva	Choroid tubercle, petechiae, Roth's spot	Disseminated granulomatosis, endocarditis
Neck and axilla	All lymph nodes including Virchow's.	Infections (Koch's, viral), sarcoidosis, SLE, metastatic cancer, lymphoma, leukemia
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective endocarditis
Abdomen	Enlarged liver; lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis
Rectum	Perirectal tenderness; prostatic tenderness	Abscess
Genitalia	Testicular nodule epididymal nodule	Polyarteritis nodosa, disseminated granulomatosis
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

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 fluroquinolone 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 justified, however one should remember that treatment should not be worse than disease. In India infections notably extra pulmonary tuberculosis is the most common cause of FUO. Noninfectious causes like collagen vascular disease and neoplasms are becoming important differential diagnosis.

REFERENCES

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore). 1961;40:1-30.
2. Harrison's Fever of unknown origin. In: Longo D, Fauci A, Kasper D (Eds). Principles of Internal Medicine, 18th edition. Mc Graw Hill; 2012. pp.158-64.
3. Druack DT, Streat AC. Fever of unknown origin reexamined and redefined. Curr Clin Top Infect Dis. 1991;11:35-51.
4. Tabak F, Mert A, Celik AD, et al. Fever of unknown origin in Turkey. Infection. 2003;31(6):417-20.
5. Gaeta GB, Fusco FM, Nardiello S. Fever of Unknown origin: a systematic review of literature for 1995–2004. Nucl Med Commun. 2006;27(3):205-11.
6. Mourad O, Palda V, Detsky AS. A comprehensive evidence based approach to FUO. Arch Intern Med. 2003;163(5):545-51.
7. Knockaert DC, Vanneste CJ, Bobloecrs JJ. Fever of unknown origin in elderly patients. J Am Geriatr Soc. 1993;41:1187-92.
8. Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J intern Med. 2003;253(3):263-75.
9. Handa R, Singh S, Singh N. Fever of unknown origin: a prospective study. Trop Doct. 1996;26:169-70.
10. Kejariwal D, Sarker N, Chakravarti SK, et al. Pyrexia of unknown origin: a prospective study of 100 cases. J Postgrad Med. 2001;47:104-7.
11. Joshi N, Rajeshwari K, Dubay AP, et al. Clinical spectrum of fever of unknown origin among Indian children. Ann Trop Pediatr. 2008;28:261-6.
12. Bandyopadhyay D, Bandyopadyay R, Paul Roy D. The etiological study of fever of unknown origin in patients admitted to medicine ward of a teaching hospital of eastern India. Journal of Global Infections Diseases. 2011; 3(4):329-33.
13. Bleeker Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicentre study of FUO: yield of structured diagnostic protocol. Medicine. 2007;86(1):26-38.
14. de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO) I. A prospective multi-centric study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore). 1997;76(6):392-400.
15. de Kleijn EM, van Lier HJ, van der Meer JW, et al. Fever of unknown origin (FUO) II. Diagnostic procedures in a prospective multi-centric study of 167 patients with FUO. Medicine (Baltimore). 1997;76(6):401-14.