CHAPTER

3

Pyrexia of Unknown Origin - Physician's Challenge

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PUO(FUO) should be reserved for prolonged febrile illnesses without an established etiology despite intensive evaluation and diagnostic testing. FUO remains a challenging diagnostic problem with all the physicians. With the development of better diagnostic techniques, the cause of fever is often found before three weeks of illness and therefore only more difficult to diagnose cases meet the definition of FUO as given in Table 1.

Table 1: Definition of PUO

Original (1961, petersdorf and Beteson)	• Temperature >101^{0}F(38.3 C) on several separate occasions • Fever lasting for more than 3 weeks • Evaluation of at least one week in hospital
Revised (1991)	• Temperature of >101^{0}F on several separate occasions • Fever lasting more than 3 weeks • Evaluation of at least 3 outpatient visits or 3 days in inpatient care
New	• Temperature >101^{0}F documented clinically on several separate occasions • Duration of illness >3weeks • Non immunocompromised (neutropaenia>1 week ,known HIV, Hypogammaglobulinaemia or use of steroids >10mg *2weeks in 3 months prior to fever • Appropriate initial diagnostic work up does not reveal the etiology of the fever(erythrocyte sedimentation rate or C-reactive protein, hemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, antinuclear antibodies, rheumatoid factor, microscopic urinalysis, ferritin, three blood cultures, urine culture, chest X-ray, abdominal ultrasonography and tuberculin skin test.

The etiologies of the PUO have changed over time because of shifting disease patterns and new diagnostic techniques. In general, infection accounts for about 20–25% of cases of PUO in Western countries; next in frequency are neoplasms and noninfectious inflammatory diseases (NIIDs). In tropical and subtropical areas(INDIA), infections are a much more common cause of PUO), while the proportions of cases due to NIIDs and neoplasms are similar. Up to 50% of cases caused by infections in patients with PUO outside Western nations are due to tuberculosis, which is a less common cause in the United States and Western Europe.

CAUSES

More than 200 causes of PUO have been described in literature. The causes for PUO are extensive, but it is important to remember that PUO is far more often caused by an atypical presentation of a rather common disease than by a very rare disease.

1. Bacterial: Tuberculosis, typhoid fever and other salmonelloses, Abdominal abscess, appendicitis, cholangitis, cholecystitis, endocarditis, epidural abscess, infected vascular catheter, infected joint prosthesis, infected vascular prosthesis, infectious arthritis, intracranial abscess, liver abscess, lung abscess, mastoiditis, osteomyelitis, pelvic inflammatory disease, prostatitis, pyelonephritis, urinary tract infection.
2. Unusual infections: Actinomycosis, atypical mycobacterial infection, brucellosis, Campylobacter infection, Chlamydia pneumonia infection, chronic meningococcemia, gonococcemia, legionellosis, leptospirosis, Lyme disease, rickettsiosis, syphilis, tick-borne relapsing fever (Borrelia duttonii), Whipple's disease (Tropheryma whipplei), yersiniosis.
3. Parasitic: Malaria, Amebiasis, babesiosis, echinococcosis, malaria, schistosomiasis, strongyloidiasis, toxoplasmosis, trypanosomiasis.
4. Viral: Dengue, coxsackie virus infection, cytomegalovirus infection, Epstein-Barr virus infection, hepatitis (A, B, C, D, E), herpes simplex, HIV infection, parvovirus infection.
5. Non infectious autoimmune diseases: Ankylosing

Table 2: Potential Diagnostic clues

Clues	Possible diagnosis
*Exposure	
• fresh water exposure • living conditions (homeless) • pets ,wild animals • recent travel to areas with endemic diseases	Leptospirosis Tuberculosis Brucellosis
*Medical history	
• Abdominal disorders • History of transfusions • Malignancy • Psychiatric illness • Recent hospitalization	Alcoholic hepatitis, HBV, HCV, HIV Metastasis Factitious fever Nosocomial infection
*High risk behavior	
• intravenous drug user	Abscess,endocarditis.
*Physical	
• rash(erythema multiforme,petechiae) • Conjunctivitis/uveitis • Hepatosplenomegaly • Polyarthralgia • Lymphadenopathy	Adenovirus,herpes,tick borne Adult stills disease,SLE Lymphoma, Leptospirosis IBD, Chikungunya Cat scratch disease,EBV,CMV

spondylitis, antiphospholipid syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behçet's disease, cryoglobulinemia, dermatomyositis, Felty syndrome, gout, mixed connective-tissue disease, polymyositis, pseudogout, reactive arthritis, relapsing polychondritis, rheumatic fever, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus.

6. Vasculitis: Allergic vasculitis, Churg-Strauss syndrome, giant cell vasculitis/polymyalgia rheumatica, granulomatosis with polyangiitis, hypersensitivity vasculitis, Kawasaki's disease, polyarteritis nodosa, Takayasu arteritis.

7. Granulomatous :Sarcoidosis

8. Autoinflammatory syndrome: Adult-onset Still's disease, CAPS (cryopyrin-associated periodic syndromes), Crohn's disease, familial Mediterranean fever, hemophagocytic syndrome, juvenile idiopathic arthritis.

9. Malignancy:

a. Haematological malignancy- Amyloidosis, angioimmunoblastic lymphoma, Hodgkin's disease, hypereosinophilic syndrome, leukemia, lymphomatoid granulomatosis, malignant histiocytosis, multiple myeloma, myelodysplastic syndrome, myelofibrosis, non-Hodgkin's lymphoma, plasmacytoma, systemic mastocytosis, vaso-occlusive crisis in sickle cell disease

b. Solid tumours - most solid tumors and metastases can cause fever. Those most commonly causing PUO are breast, colon, hepatocellular, lung, pancreatic, and renal cell carcinomas

10. Defective thermoregulatory causes: Brain tumor, cerebrovascular accident, encephalitis, hypothalamic dysfunction

11. Drug Fever: Barbiturates, carbamazepine, phenytoin, Carbapenems, cephalosporins, erythromycin, Isoniazid, Minocycline.

STUDIES

Evaluation

The most important and primary approach to these patients are thorough history taking, proper clinical examination and obligatory investigations. PDCs are defined as all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis are given in Table 2.

History: The history should include information about the fever pattern (continuous ,intermittent ,remittent or recurrent) and duration, previous medical history, present and recent drug use, family history, sexual history, recent and remote travel, unusual environmental exposures associated with travel or hobbies, and animal contacts.

One of the first steps should be to rule out factitious or fraudulent fever, particularly in patients without signs of inflammation in laboratory tests. All medications, including nonprescription drugs and nutritional supplements, should be discontinued early in the evaluation to exclude drug fever

Physical examination: special attention to the eyes, lymph nodes, temporal arteries, liver, spleen ,sites of previous surgery, entire skin surface, and mucous membranes.

In patients without PDCs or with only misleading PDCs, fundoscopy by an ophthalmologist may be useful in the early stage of the diagnostic workup.

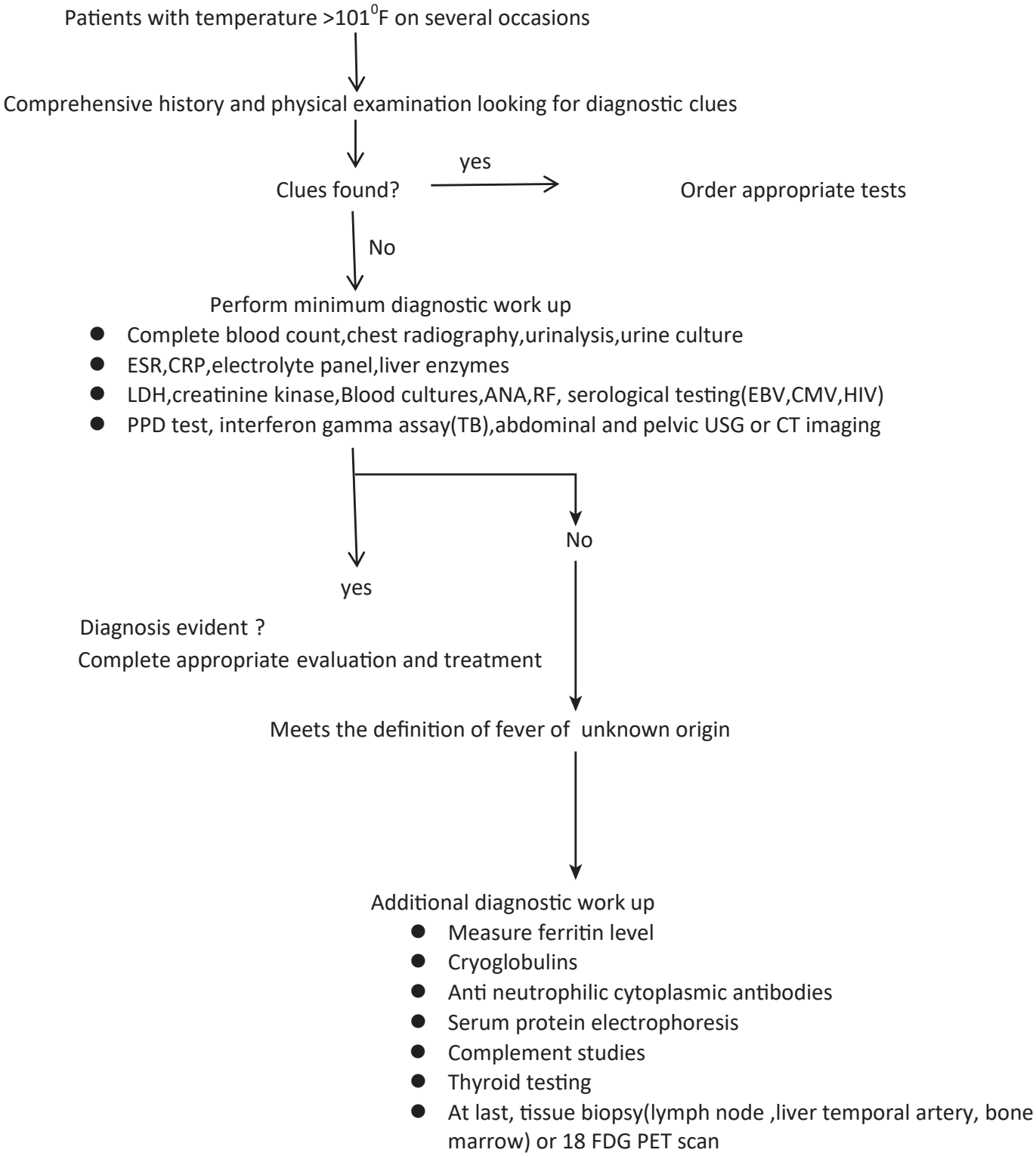
FDG PET SCAN

FDG-PET is based on the increased uptake of FDG (fluorodeoxyglucose) by activated inflammatory cells, which occurs in infection, NIID and malignancy. FDG-PET/CT is a non-invasive imaging technique with high diagnostic yield and should therefore be performed early in the investigation of FUO. FDG-PET was helpful in 40% and FDG-PET/CT in 54% of cases. But in countries like India where FDG PET scans are not readily available ,relatively more cases of PUO remains undiagnosed.

TREATMENT

The emphasis in patients with PUO is on continued observation and examination with avoidance of "Shotgun" empirical therapy. However, vital signs instability or neutropenia is an indication for empirical

Approach to patients of pyrexia of prolonged duration



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. Effects of glucocorticoids on temporal arteritis and polymyalgia rheumatica and granulomatous hepatitis are equally dramatic. Steroids are not to be given early in the course as they may mask various PDCs of the diseases. In patients with a suspected autoinflammatory disorder the interleukin-1 receptor antagonist, anakinra, can be tried. Remission of symptoms is expected within 24–48 hours. If anakinra is ineffective after two weeks of treatment,

a beneficial effect should not be expected and the drug should be stopped.

Patience, compassion, equanimity, vigilance and intellectual exibility are indispensable attributes for the clinician in dealing successfully with PUO.

PROGNOSIS

The overall prognosis of FUO is determined by the underlying disease. In patients in whom no cause of FUO can be established, prognosis is generally good and mortality is low. Up to 75% of patients experience spontaneous remission of fever, although this may take a long time. Treatment with NSAIDs or corticosteroids increases this proportion even further.

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