Case Discussion in Medicine

Approach to a case of Pyrexia of Unknown Origin (PUO)

Uttam Biswas[1], Pallavi Mahato[2], Milan Chakraborty[3]

Fever is one the most common presenting symptoms in our daily practice both in OPD or IPD but sometimes it becomes the diagnostic challenge for most clinicians with differentials running in hundreds. Pyrexia of Unknown Origin (PUO) reserved for those febrile illness in which no diagnosis could be reached in spite of extensive investigations. In most of the time it is very challenging to diagnose a case of true PUO, specially in a resource limited country like India. Thorough history and clinical examination is very important to find out potentially diagnostic clues (PDCs) and it is very useful for further evaluation .In this article we have outlined the latest approach to diagnosed a case of pyrexia of unknown origin (PUO). So this article will be very useful for the physicians to evaluate a case of Pyrexia of unknown origin. (PUO).

[*J Indian Med Assoc* 2021; **119(2):** 46-9]

Key words **: Pyrexia of Unknown Origin (PUO) , Approach,Evaluation.**

Fever may be the most common presentation in OPD/IPD but is the most intriguing diagnostic challenge for most clinicians with differentials running in hundreds. Most fevers usually resolve even prior to a proper diagnosis can be reached or develop additional features that help localise the cause. Pyrexia of Unknown Origin (PUO) also known as Fever of Unknown Origin (FUO), reserved for those febrile illness in which no diagnosis could be reached in spite of extensive investigations. In a resource limited country like India it difficult to diagnose a case of true PUO, thorough history and clinical examination is very useful for further work up. So this article will be very useful for the evaluation of a case of Pyrexia of unknown origin (PUO).

Definition :

In 1961, Petersdorf and Beeson first coined the term "fever of unknown origin" defined it as temperature more than 38.3°C (101°F) on two occasions and duration of fever more than 3 weeks but failure to reach to diagnosis despite 1 week of inpatient investigation.[1] Later on inpatient management was provided only to patients requiring hospitalisation, hence the latter part of the definition had to be excluded.

Later on, In 1991,Durack and Street [2] classified PUO into 4 types:

- Classical
- Nosocomial
- Neutropenic
- HIV

Minimum 3 OPD visits or 3 days of in hospital investigation is needed before classifying a case as PUO.

Nowadays, PUO is defined as:[3]

- Fever more than 38.3°C (101°F) on atleasttwo occasions
- Illness duration of more than 3 weeks
- No known immunocompromised state
- Diagnosis that remains uncertain after a thorough history taking, physical examination, and the following obligatory investigation-determination of ESR, CRP, platelet count, leucocyte count, differential count, haemoglobin level, electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibody and rheumatoid factor; protein electrophoresis; urine analysis; blood culture(n=3); urine culture; chest xray; abdominal usg; and tuberculin skin test or interferon gamma release assay.

Causes of PUO :

The possibilities can be extensive and with the various studies it has been postulated that PUO is more often caused by an atypical presentation of common diseases rather than by a very rare disease.[4] The original categories for the diseases that cause classic PUO are still the same. These are:

- Infectious
- non-infectious inflammatory disease (NIID)
- neoplastic
- miscellaneous (fraudulent fever, factitious fever, drug fever, etc)

The most common causes of each category are described in the table here:[5] Infection is much more common cause of PUO in India as compared to western world (43% vs.17%) and tuberculosis accounts for 50% of those infections.[6]

Approach to the Patient :

As because a wide variety of etiology may cause PUO, a stepwise approach consisting of two phases is followed. PUO related mortality has decreased immensely to around 10% as most cases are due to some treatable cause. Malignancy is usually responsible for most mortality especially NHL.

First Stage Diagnostic Test :

The most important step is to search for potentially diagnostic clues (PDCs) that will point towards a diagnosis. PDCs are defined as all localising signs, symptoms and abnormalities through repeated history taking, thorough clinical examination and obligatory investigations listed below.

History **:** should include information about

- Fever pattern and duration

[1]MD (Medicine), MRCP(UK), Assistant Professor, Department of Medicine, Burdwan Medical College and Hospital, Purba Burdwan 713104

[2]MD (Medicine PGT), Junior Resident, Department of Medicine, Burdwan Medical College and Hospital, Purba Burdwan 713104

[3]MD (Medicine), Professor, Department of Medicine, NRS Medical College and Hospital, Kolkata 700014

Received on : 05/02/2021
Accepted on : 08/02/2021

Infectious	Non Infectious Inflammatory Disease	Neoplastic	Miscellaneous
Bacterial • Occult abscess • Complicated urinary tract infection • Culture negative • endocarditis • Osteomyelitis • Tuberculosis • Coxiellaburnetti (Q fever) • Rickettsial infections • Enteric fever • Brucellosis **Viral** • Epstein–Barr virus • Cytomegalovirus • Human immuno-deficiency virus **Parasitic** • Malaria • Visceral leishmaniasis • amebiasis • Toxoplasmosis **Fungal** • Histoplasmosis • Aspergillosis • Crytococcosis	• Giant cell arteritis • RA • Sarcoidosis • Adult Still's disease • Systemic lupus erthymatosus • Polyarteritisnodosa • Granulomatosis with polyangitis (Wegener granulomatosis) • Familial Mediterranean fever	• Non-Hodgkin lymphoma • Leukaemia • Renal cell carcinoma • Hepatocellular carcinoma • Metastatic lesions (commonly hepatic metastasisfrom adenocarcinomas • Hyperthyroidism • Factitious fever	• Drugs (antibiotics, antiepileptic, NSAID, antriarrthymic) • Cirrhosis • Pulmonary embolism and DVT • Inflammatory bowel disease • Endocrine disease

Source : Wassimabdelwahab E Pyrexia of Unknown Origin: current perspective. IJBR 2019; ***10(1):*** *e4987.*

- Previous medical and surgical history
- Recent drug history
- Family and sexual history
- Recent or remote travel
- Unusual environmental exposures associated with travel or hobbies and animal contacts

Physical Examination : Complete and repeated physical examination to search for the PDCs must include-

- Examination of eye and fundoscopy
- Skin
- Lymph nodes
- Temporal arteries
- Liver and spleen

1st stage investigation : Investigations discussed in the new definition are obligatory , however further biochemical testing may lead to a definitive diagnosis.[6] Before diagnostic tests are initiated all drugs must be stopped including steroids or antibiotics which can mask may diseases as well as rule out drug fever. PDCs are a diagnostic suspicion which represent after an initial workup (Fig 1).With a directed personalized approach, few additional investigations are to be done to confirm the suspicion according to the Fig 1.

When PDCs have been obtained, a list of differential diagnosis have to be formed and specific tests are performed to confirm them. If PDCs are absent or guided tests come out to be negative, following investigations.

- Cryoglobulin
- Fundoscopy
- FDG-PET/ gallium scan/ labelled leucocyte scintigraphy .If used at an early stage FDG-PET/CT can be cost effective diagnostic tool in establishing an early diagnosis, reducing hospital stay and decreasing the use of unnecessary testing.[7]If fever persists after discontinuation of drugs for at least 72 hours ,scintigraphy or FDG-PET/CT should be performed.[3]

Potential diagnostic clues and possible etiologies:[8]

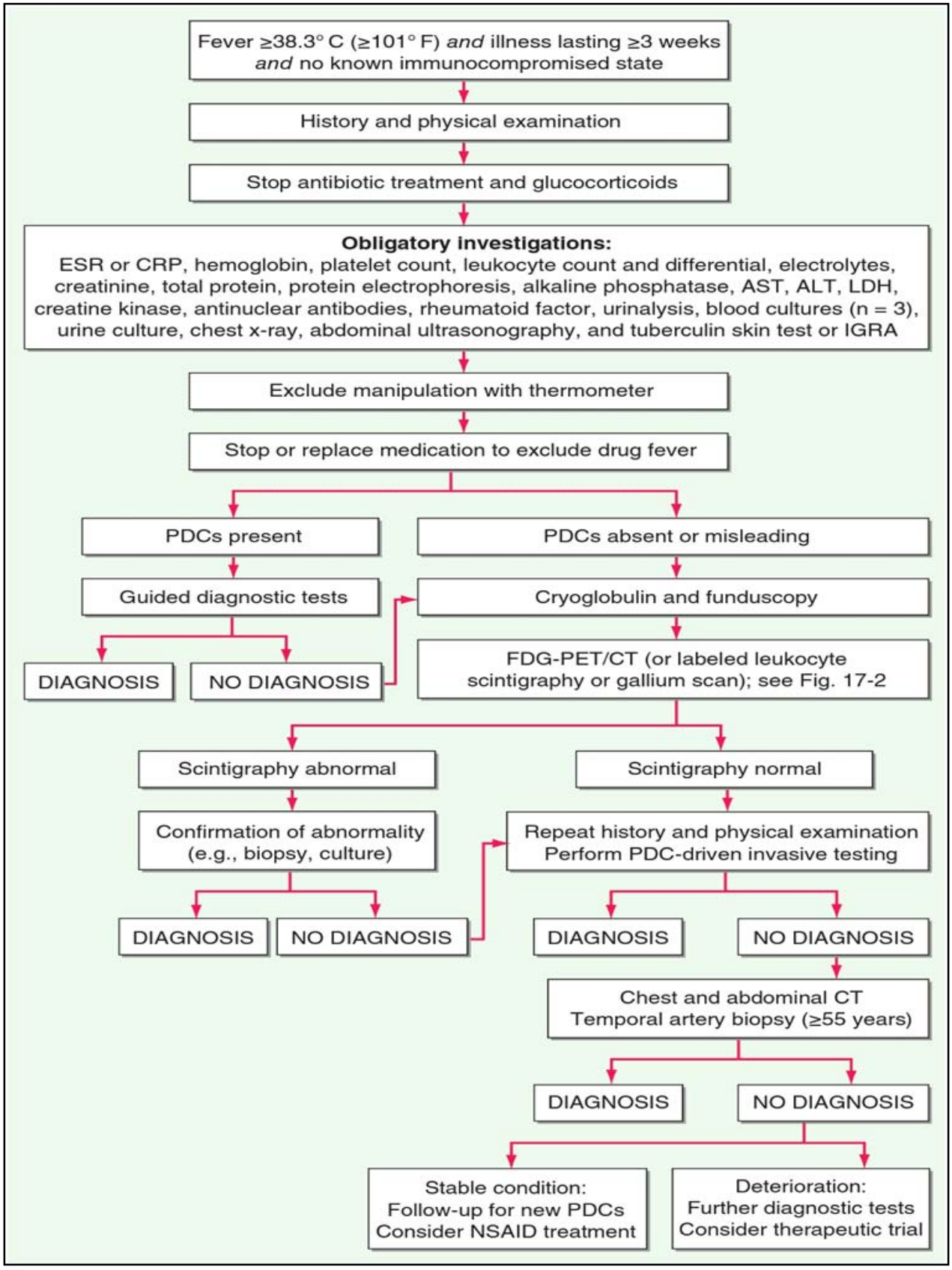
Later stage diagnostic tests :

Scintigraphicor FDG PET / CT abnormalities need to be confirmed by pathology or culture biopsy of specimen.[6]If no diagnosis can be reached, reconsidering history and physical examination to search for PDCs followed by invasive guided testing to be done. If still nothing can be found, the following 3 tests to be done.

- Chest CT
- Abdominal CT
- Temporal artery biopsy (>55 years)

Biopsy is considered to be an important diagnostic modalities in the second stage diagnostic testing. It includes temporal artery biopsy liver biopsy, lymph node biopsy, pleural biopsy, pericardial biopsy, bone marrow biopsy.[9,10] If no diagnosis can be reached till now then further follow up to be done for new PDCs if patient is stable or consider for therapeutic trial if patient is deteriorating.

PDCs	Possible Etiology
• Unintentional wt loss	• Neoplastic process • Tuberculosis • Brucellosis
• Drenching night sweats	• Haematological malignancy • tuberculosis
• joint pain (early morning)	• inflammatory arthritis
• unilateral retroorbital headache, jaw claudication,	• giant cell arthritis
• history of steroid use, surgeries, prosthetic material	• occult abscesses
• history of smoking	• malignancy
• prolonged immobility, OCP	• thromboembolic disease
• recent change of medication	• drug fever


Fever ≥38.3° C (≥101° F) and illness lasting ≥3 weeks and no known immunocompromised state
History and physical examination
Stop antibiotic treatment and glucocorticoids
Obligatory investigations:
ESR or CRP, hemoglobin, platelet count, leukocyte count and differential, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, AST, ALT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n = 3), urine culture, chest x-ray, abdominal ultrasonography, and tuberculin skin test or IGRA
Exclude manipulation with thermometer
Stop or replace medication to exclude drug fever
PDCs present
PDCs absent or misleading
Guided diagnostic tests
Cryoglobulin and funduscopy
DIAGNOSIS
NO DIAGNOSIS
FDG-PET/CT (or labeled leukocyte scintigraphy or gallium scan); see Fig. 17-2
Scintigraphy abnormal
Scintigraphy normal
Confirmation of abnormality (e.g., biopsy, culture)
Repeat history and physical examination
Perform PDC-driven invasive testing
DIAGNOSIS
NO DIAGNOSIS
DIAGNOSIS
NO DIAGNOSIS
Chest and abdominal CT
Temporal artery biopsy (≥55 years)
DIAGNOSIS
NO DIAGNOSIS
Stable condition:
Follow-up for new PDCs
Consider NSAID treatment
Deterioration:
Further diagnostic tests
Consider therapeutic trial

Treatment :

As a norm empirical therapy is to be avoided as that may change the clinical picture and definite diagnosis can never be reached. Emperical therapy with antiobiotic, ATD or glucocorticoid should be started only in certain conditions as given below:

- *Antibiotics* : hemodynamic instability and neutropenia, empirical antibiotic to be started.
- *Antitubercular drugs* : If TST or IGRA is positive or if granulomatous disease is present but sarcoid seems unlikely; a trial of ATD may be done. If fever doesn't resolve after 6 weeks of ATD, alternate diagnosis to be considered.
- *Colchicine :* may be tried in patients with symptoms compatible with familial mediterranena fever, especially those residing in high prevalence regions.
- *NSAIDS:* when dramatic response to NSAID is seen, adult onset stills disease may be a diagnostic possibility.
- *Glucocorticoids:* similar dramatic response is seen in giant cell arteritis and polymyalgia rheumatica.
- *Anakinra:* therapeutic trial of this IL1 antagonist may be considered in patients whose PUO has not been diagnosed after later stage diagnostic testing. Anakinra remains free from adverse effects associated with steroid but with a better control.

The ability of immunosupressants to be able to mask fever yet allowing the spread of infection or lymphoma enforces that their use to be avoided until infectious disease/ malignancy is ruled out and inflammatory disease is a strong suspicion and is organ/life threatening.

Conclusion :

With the greater understanding of the PUO and easy accessibility tothe wide range of investigations both non invasive and invasive, now a days majority of PUO cases can be diagnosed but still it is a diagnostic challenge.It is highly recommended to search for uncommon manifestation of a common disease rather than common manifestations of an uncommon disease. Despite promising newer technologies, detailed and repeated history, thorough clinical examination and baseline investigations still remain the cornerstone to reach at a definitive diagnosis.

References

1 Petersdorf RG, Beeson PB — Fever of Unexplained Origin: Report on 100 cases. *Medicine* 1961; 401-30.

2 Durack DT — Fever of unknown origin -re-examined and redefined.*Curr Clin Top Infect Dis* 1991; **11:** 35-51

3 Patro S — Approach to a case of pyrexia of unknown origin: What's New in 2020.Medicine Update 2020. Japee brothers medical publishers Vol. 30; Chapter 203; 871-74.

4 Bleeker-Rovers CP, Vos FJ, De Kleijn EM — A prospective multicenter study on Fever of Unknown Origin: the yield of a structured diagnostic protocol Medicine 2007; **86(1):** 26-38.

5 Wassimabdelwahab E — Pyrexia of Unknown Origin: current perspective. *IJBR* 2019; **10(1):** e4987.

6 Fauci AS, Jamesson JL, Kasper DL — Harrison's principles of internal medicine,20 th edition New York : McGraw Hill, Health Professions Divission 2018. 114-22.

7 Nakayo EB, Vicente AG, Castrejon AS — Analysis of cost-effectiveness in the diagnosis of fever of unknown origin and the role of 18F-FDG PET-CT: A proposal of diagnostic algorithm.Revista Espanola de medicina nuclear eimagen molecular(English edition) 2012; **31(4):** 178-86.

8 Beresford RW, Gosbell IB — Pyrexia of unknown origin: causes, investigation and management. *Int Med J* 2016; **46(9):** 1011-6

9 Rupali P, Garg D, Viggweswarupu S — Etiology of Classic Fever of unknown origin (PUO)among immunocompetent Indian adult. JAPI 2019; **67:** 21.

10 Jha A, Sarda R —Value of bone marrow examination in pyrexia of unknown origin. *J Pathol Nepal* 2013; **3(6):** 447-51.