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Case Reports : Pyrexia Of Unknown Origin: Balancing Patient's Calls Vs Protocols

M Mohamed Fawaz [1]
[1] *(Internal Medicine Specialist, Starcare Medical Centre ,Sharjah , UAE ; Previously - Consultant , Department of General Medicine , Meenakshi Hospital , Tanjore, India)*

Abstract :
The article explores the complex diagnostic landscape of Pyrexia of Unknown Origin (PUO) and its evolution over time. It highlights the significance of indirect clues in diagnosis. Three case reports illustrate the challenges and successes in managing PUO. The cases underscore the dynamic nature of medical conditions and the value of reinvestigating variable factors. The article also discusses the implications of toxic vacuolization in white blood cells, the persistence of toxic vacuolations in treated patients, and the reverse approach of deriving diagnostic clues from therapeutic responses. The study concludes by highlighting the ongoing advancements in diagnostic methodologies and the nuanced considerations in managing undiagnosed PUO cases.

Keywords :*Pyrexia of Unknown Origin (PUO), Elevated body temperature criteria, Hyperpyrexia*

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I. Introduction

Definition of PUO as per 1961 [1] : 3 weeks of undiagnosed fever (38.3 C / 101 F) , In spite 1 week Inpatient evaluation or 3 Outpatient follow up visits

Knowing the Definitions

Elevated temperature	Definition and causes
Fever	Rectal temperature above 100.4°F (38°C) , Oral temperature above 100°F (37.8°C) Axillary (armpit) temperature above 99°F (37.2°C) , Ear (tympanic membrane) temperature above 100.4°F (38°C) in rectal mode or 99.5°F (37.5°) in oral mode, Forehead (temporal artery) temperature above 100.4°F (38°C)
Hyperpyrexia	Core Body Temperature greater Than Or Equal To 40.0 Or 41.5 °c (104.0 Or 106.7 °f) [Brain Damage, Intracranial Hemorrhage, Drug Overdose-Toxin-Poisoning, Thyroid Storm, Serotonin Syndrome, Neuroleptic Malignant Syndrome,]
Hyperthermia	temperature greater than 37.5–38.3 °C (99.5–100.9 °F) External Causes : Heat Stroke , Stimulants , Hallucinogens , Cocaine

Justification for Criteria in Defining a Pyrexia of Unknown Origin (PUO):

Criteria	Reason
Temperature Criteria > 38.3 C / 101 F Or More	Exclude Patient With Normal Variable Temperature
3 Week Duration	For Acute Infections To Declare Itself Or Settle Spontaneously
Inpatient Evaluation for 1 Week /Or 3 Outpatient Visits	For Sufficient Time For Investigations, Imaging , Cultures, Blood Tests

A Paradigm Shift and Redefinition:Unknown Origin to Multiple Origins

Fevers Defying Explanation Despite Ongoing Antibiotic Treatment such as Patients on mechanical ventilation, those with decubital ulcers, deep vein thrombosis (DVT), and individuals with urethral/central/peripheral catheters, drug-induced fevers, cutaneous eruptions or erythema, abdominal distension, and wounds with serous discharge albeit non-purulent are now contributors to the expanding spectrum of fever etiologies.Pyrexia of Unknown Origin (PUO) was later classified into distinct categories [2], namely classic, nosocomial, neutropenic, and HIV-associated, based on criteria such as temperature, duration of hospital stay,

evaluation period, neutrophil count, and the presence of HIV infections. Within each category, etiologies were meticulously narrowed down, encompassing a spectrum of possibilities, and this comprehensive categorization aids in precise diagnostic and therapeutic approaches for patients with PUO.

II. The Basics

Classical example : 3 months of FEVER

A Non-Resident Indian gentleman in his mid-40s, hailing from Singapore, sought medical evaluation after experiencing three months of persistent fever. Despite the escalating frequency of febrile episodes, the patient presented an intriguing case, devoid of additional complaints such as chills, rigors, or myalgia. Notably, the fever, initially occurring twice a month, intensified to frequent occurrences within a week. Detailed investigations conducted in Singapore, the patient's country of residence, proved inconclusive, with comprehensive tests including CBC, RFT, LFT, blood cultures, urine cultures, echo, CT abdomen, X-ray, and viral markers, along with various serology assays failing to reveal an underlying cause. Remarkably, general physical examinations and systemic evaluations yielded normal results. The patient was subsequently discharged with antipyretic medications and reassurance. But the symptoms persisted for which the patient had flown back to India and visited our healthcare facility **(case report to be continued in subsequent sections)**. This diagnostic enigma, highlights the complexity and challenges associated with unraveling the mysteries of PUO.

What to suspect ?

When faced with fevers of unknown origin, one should consider a spectrum of potential etiologies encompassing classical culprits like bacterial, spirochetal, rickettsial, chlamydial, viral, fungal, and parasitic infections, as well as neoplastic and inflammatory conditions. Additionally, a range of miscellaneous factors, including drug-induced reactions, Munchausen syndrome, disordered heat homeostasis (central fever), endocrine disorders, emboli, and other diverse causes, should be contemplated within the diagnostic framework.

What do we know ?

1. Approach to PUO is characterized by the absence of a standard diagnostic algorithm, presenting a challenge in the formulation of a systematic approach.
2. With over 200 potential differentials, the majority of cases are attributed to infectious, autoimmune, or malignancy-related causes, emphasizing the multifaceted nature of the condition. [3]
3. Demographic considerations play a crucial role in identifying potential infectious diseases, necessitating a comprehensive assessment of patient characteristics.
4. It is noteworthy that up to 50% of individuals with classical PUO are discharged without a definitive diagnosis, underscoring the complexity and difficulty in pinpointing the root cause.[4]
5. Invasive procedures are recommended only when clinically justified, highlighting the importance of a careful and selective approach to intervention.
6. Despite the challenges in diagnosis, a positive aspect is that a significant portion of undiagnosed cases exhibits a favorable prognosis, offering some reassurance in the management of classical PUO.

What is agreed upon ?

1. In the absence of an identified cause, the prescription of antipyretic drugs is a viable option to alleviate fever symptoms.
2. Caution is advised against the use of corticosteroids in cases of undiagnosed PUO.[5]
3. The administration of empirical antibiotic therapy is not considered appropriate for patients with PUO, emphasizing the importance of targeted and evidence-based treatment.
4. In scenarios where extrapulmonary tuberculosis (TB) is suspected, empirical therapy with antituberculosis drugs may be considered as a therapeutic trial. However, this approach should be carefully weighed, particularly when the likelihood of obtaining a positive mycobacterial culture is limited.

Note: Rifampicin, a component of antituberculosis regimens, possesses the potential to suppress fever in various conditions, including brucellosis and osteomyelitis. This highlights the need for careful consideration of differential diagnoses and the broader clinical context when implementing therapeutic interventions in cases of undiagnosed PUO.

III. The Core Challenge

Protocols : Our Diagnostic arsenal

Navigating a case of Pyrexia of Unknown Origin (PUO) involves a step-by-step approach encompassing routine tests like CBC, sugars, urea, creatinine, liver function, urine and stool analysis, chest X-ray, HIV serology, blood culture, Mantoux test, malaria antigen, and blood CRP. Further, systemic-specific investigations delve into respiratory, gastrointestinal, autoimmune, genitourinary, hematological, and neurological aspects, each

demanding a specialized set of evaluations. In cases where the system involvement remains elusive, a meticulous revision of history and records, alongside specific tests for thyroid antibodies, prostatic massage study, high vaginal swab, repeat AFB culture, filarial antigen, Brucella blood culture, EBV & CMV antigen, and implants exploration is warranted. If still inconclusive, gallium scans or continual follow-up for evolving features and exploration of other sites like dental, skin, lacrimal gland, ear, and osteomyelitis become imperative. This exhaustive list underscores the challenges inherent in approaching a PUO case, highlighting the intricate nature of diagnostic protocols.

Problem with Protocols

1. How extensive to investigate
2. How often to repeat the investigations
3. How to respond to false positives

Patient's call vs Protocols

Patient's call	Protocol
Demands fast treatment for prolonging symptoms.	Advises : Do not start on empirical treatment
Increasing Anxiety among family members.	Reinforces to : Investigate until a cause is found.
Financial Constraints for the investigations as well as lack of employment due to ongoing symptoms.	Medical Negligence Aspects - the risk of overlooking or undermining findings that seem inconsistent with clinical scenario
Lack of Time due to their personal responsibilities.	Concern to avoid unwarranted treatment for False positives reports

In this symphony of challenges, the physician is both conductor and performer, orchestrating a delicate balance between the demands of compassion, adherence to protocols, and the unforgiving constraints that accompany the pursuit of answers in the realm of PUO.

IV. Case Reports

Key takeaways from the below case reports are as follows:

1. *From the vast diagnostic reports , a single abnormal investigation finding may provide a valuable diagnostic clue. At this point in the absence of supportive evidence and based on clinical experience alone , treatment may be initiated towards the suspicious cause. A positive response to therapy should help us in narrowing down or affirming our clinical diagnosis.*
2. *It is crucial to avoid binding ourselves to previous diagnosis or preformed opinions bearing in mind that various differential diagnoses may clinically present with similar symptoms.*
3. *Although the patient could have been extensively evaluated at another medical facility , it is crucial not to rely completely on previous investigation reports and draw conclusions , on the contrary clinical suspicion must be vigilant and variable factors should be reinvestigated as it may unmask evolving clues to diagnosis.*

Case Report 1 (continued) **:** 3 months of Fever

Patient presentation at our center after management elsewhere :

Patient Profile: Mid-40s, Married with one child, Singaporean NRI

Chief Complaints: Three months of persistent fever, without any accompanying symptoms

Relevant History:Cyclical recurrent fevers, initially occurring twice a month and later increasing to frequent episodes within a week

Associated Symptoms: No chills, rigors, myalgia, or symptoms related to any specific organ system

Clinical Signs: General physical examinations and systemic examination revealed no abnormalities

Investigation Reports: CBC, RFT, LFT, blood cultures, urine cultures, echocardiogram, CT abdomen, X-ray, viral markers, and select serology assays which had been done outside provided no conclusive findings.

Outside Diagnosis: PUO, managed with antipyretic therapy, as no definitive cause for the recurrent fevers was identified. - BUT PATIENT STILL SYMPTOMATIC.

Course in our Hospital:

On arrival: Patient landed in India and visited our healthcare facility appearing normal in general observation. History , previous reports were analyzed and general and systemic exams performed.

Initial Findings: Additional workup done showed Normal RA, ANA, and Sr. Procalcitonin levels; Peripheral smear showed toxic vacuoles (only positive finding)

Diagnosis: Suspicious of Infective Etiology: Given the clinical presentation of patient and clinical experience in presence of toxic vacuoles in sepsis patients , an infectious etiology was suspected.

Treatment: Though we could not isolate the organism in blood culture and clinical stability of the patient did not warrant hospital admission evaluation, the patient was administered a seven-day oral course of FEROPENEM and LINEZOLID.

Follow-up After One Week: Subsequent assessments revealed no fever episodes, and in repeat peripheral blood smear the toxic vacuoles disappeared.The patient was advised to continue antibiotics for an additional five days (Extended Antibiotic Course)

Follow-up After 5 days : At the follow-up, the patient reported no complaints and was preparing to return to Singapore.

Long-Term Follow-Up, One-Year Review in OPD: The patient presented for a follow-up after one year, reporting no history of fever and overall comfort.

Inference: In spite of being extensively investigated without a conclusion elsewhere, the case emphasizes the importance of recognising indirect clues, such as toxic vacuoles in the peripheral smear pointing towards occult sepsis in our case , in reaching a diagnosis.The positive response to antibiotic therapy further supports the approach we have taken in this case. This underscores the need for observations beyond conventional parameters.

Case report 2 : 2 months of PUO
Patient presentation at our center after management elsewhere :

Patient Profile: 40 years, Female , Hailing from the surrounding villages of Tanjore, India
History and Symptoms: Intermittent fever with joint pain persisting for 2 months.
Other Associated Symptoms: Nil
Clinical Examination: General physical exam and systemic exam revealed normal examination findings.
Previous Treatment: Multiple antibiotic courses, Administration of steroids and painkillers.
Outside Diagnosis: Viral fever with reactive arthritis.

Course in our Hospital:

On arrival: Patient presented in psychological distress due to failed attempts in resolving her fever and joint pain besides multiple treatment undergone.

Diagnostic Workup: Comprehensive investigations were conducted, including CBC, chest X-ray, USG abdomen, blood culture, urine culture, and serum procalcitonin were reported normal, Peripheral blood smear revealed toxic vacuoles.

Treatment Initiation: The patient was treated with a combined course of FEROPENEM and LINEZOLID orally for one week, due to the possibility of occult sepsis evidenced by toxic vacuoles in peripheral smear.

Follow-up Investigations: Patient was free from fever **.** Repeat peripheral blood smear indicated the absence of toxic vacuoles . **But Patient had persistent multiple joint pain (including small joints)**

Arthritis workup: ANA, ANCA, RA, anti CCP returned negative results, **only elevated CRP alone positive finding.**

Clinical Diagnosis : The patient was clinically diagnosed as seronegative arthritis based on clinical findings.

Initiation of DMARDs: DMARDs (Disease-Modifying Antirheumatic Drugs) were initiated as part of the treatment plan.

Follow-up Progress: No recurrence of fever was reported during subsequent evaluations., Patient had good improvement in terms of resolution of joint pain , CRP levels showed a decreasing trend, indicative of positive therapeutic response.

Further Expert Opinion : Decreasing the DMARDS dose - lead to increase in joint pain symptoms and consequent elevation in CRP levels , Patient was further referred to Rheumatologist for expert opinion

Patient Comfort: The patient reported overall comfort and improvement in symptoms on the course of treatment with seronegative arthritis.

Inference: From what was thought to be Viral Fever with Reactive Arthritis , the patient benefited with our approach wherein we aligned our diagnosis as Sepsis with Seronegative arthritis. By merely realigning our diagnosis and our understanding of the patients symptoms , the management course changed considerably, alleviating the patients symptoms significantly and identifying the cause of fever and joint pain.

Case report 3 : 22 days of PUO in shock
Patient presentation at our center after management elsewhere :

Patient Profile: 35 years, Female, Married, Accompanied by her husband.

Chief Complaints: Fever persisting for 20 days in shock requiring inotropes , Treated in the above clinical state at two different hospitals outside and referred here for further management

Past Medical History: Previously treated for TB adenitis with completed Anti-Tubercular Treatment (ATT)

Clinical Examination: Multiple small swellings on thighs with no warmth, normal skin appearance, no discharges, no joint pain, no involuntary movements, and no rash., No signs of meningism, sore throat, palpitations, or dyspnea.Patient maintained saturation in room air but required inotropes.

Previous Reports: Cultures, scans, and Echo were reported as normal (inconclusive)., Previous ASO (Antistreptolysin O) titer: 200. Elevated Total WBC count noted.

Course in our Hospital:

Diagnostic Workup: Repeat cultures and blood tests returned negative, with only an elevated total count.

Treatment Initiation: Continued treatment with Meropenem and inotropes. And planned for antibiotic escalation. *(Patient's attendants reported the fever responds only to Meropenem as per their previous treatment experiences at outside hospitals)*

Repeat ASO Titer: ASO titer elevated to 1600.

Diagnosis: Suspected acute streptococcal infection.

Antibiotic Adjustment: Antibiotics changed to Injection Penicillin G IV (4 million units IV TDS) and escalated to 6 million units TDS.

Patient Response: Significant recovery from shock, and fever ceased within 24 hours - 36 hours of initiation. Shifted out of HDU to ward

Follow up : ASO titer fell to 800, Transition to Oral Penicillin

Further OP follow up :ASO titre follow up and Oral Penicillin tapered and stopped. Last ASO titer: Negative.

Inference: This case underscores the importance of reevaluating a patient's condition, even if extensively evaluated at previous medical facilities. The patient's persistent fever, shock, and previous history of TB adenitis were initially challenging. However, a thorough diagnostic workup, including **repeat ASO titers**, unmasked a suspected acute streptococcal infection. Adjusting the antibiotic regimen to Penicillin G IV resulted in a significant recovery, cessation of fever, and a subsequent decrease in ASO titers. The case highlights the dynamic nature of medical conditions and the need to reconsider variable factors, as they may provide essential insights that were initially overlooked.

V. Clinical Inferences

1. **Implication of Toxic Vacuolization in WBCs:** The presence of toxic vacuolization in white blood cells signifies a potential manifestation of sepsis, suggesting the need for consideration of more potent antibiotic regimens.
2. **Persistence of Fever with Toxic Vacuolization in Peripheral smear in Patients previously on Antibiotics.:** In cases where patients who are on extensive antibiotic therapy but still have one and off fever , the persistence of toxic vacuolations may serve as a crucial indicator of ongoing sepsis, especially when other sepsis markers have returned to normal levels.
3. **Reverse Approach :** Diagnostic clues can be obtained from assessing how the patient responds to medications when given on clinical suspicion and positive therapeutic response should aid us in narrowing down the diagnostic puzzle.
4. **Value of Repeating Investigations in PUO:** Vigilant Suspicion and the repetition of diagnostic investigations in cases of Pyrexia of Unknown Origin (PUO) has proven to be instrumental, revealing new insights and understanding the evolving nature of the clinical symptoms.
5. **Role of Penicillin G in Antibiotic Resistance Scenarios:** Despite the utilization of higher antibiotics, Penicillin G continues to exhibit its efficacy as a gold standard in the management of fever that remains unresponsive to advanced antibiotic interventions. This observation underscores the enduring relevance of Penicillin G in antibiotic-resistant scenarios.

VI. Tweaks & Trends

Fever patterns :

In the realm of fever patterns, distinct patterns offer valuable inferences. A longer duration tends to lower the probability of an infectious origin, although one study suggests no significant correlation. In the context of Indian demographics, infections such as TB, Melioidosis, Infective Endocarditis, Enteric fever, Visceral

leishmaniasis, Lepra reaction, and Brucellosis become more probable. Continuous fever may indicate lobar pneumonia, typhoid, urinary tract infection, infective endocarditis, brucellosis, and typhus. A step-ladder pattern is characteristic of typhoid, while intermittent fever points to malaria. Remittent patterns are associated with typhoid fever and infective endocarditis. The combination of low-grade fever and night sweats suggests extra-pulmonary TB. These fever patterns offer crucial diagnostic clues, emphasizing the nuanced nature of infectious diseases and the diverse clinical presentations they manifest.

Naproxen Test

When Naprosyn (Naproxen 375 mg twice daily), is given for 3 days, Fevers due to cancers display a rapid and sustained decline while little or no change is observed in fevers due to infectious diseases. [6]However, Naprosyn test is unhelpful in differentiating neoplastic from noninfectious disorders such as connective tissue diseases

Ferritin

Most underutilized test in PUO , Elevations of serum ferritin levels are often ignored due to ferritin acting as an ―acute phase reactant. In a patient with PUO, by definition, the process is no longer acute, and elevations in the serum ferritin level take on a very different significance. An elevated ferritin level in prolonged febrile illness may indicate malignancy (especially myeloproliferative disorders) and other noninfectious inflammatory diseases, such as JRA, SLE or temporal arteritis [7].

PET-CT

Now in the first line of investigations. FDG-PET is based on the increased uptake of FDG (fluorodeoxyglucose) by activated inflammatory cells, which occurs in infection, NIID and malignancy .Allows the matching of inflammatory lesions with a precise anatomical location. Sensitivity and specificity of PET-CT for PUO were 93.8% and 80%, respectively with high positive predictive value 93% and negative predictive value (100%) [8]. Labeled leukocyte scintigraphy or gallium scintigraphy can be used as alternatives when FDG-PET/CT is unavailable.

Disadvantages : high radiation doses, relatively high cost, limited availability, high rate of false positive results ,Inability to detect systemic / nonfocal disease.

16s rRNA Sequencing, multiplex respiratory virus PCR

Two advanced diagnostic techniques, 16s rRNA Sequencing and multiplex respiratory virus PCR, are revolutionizing microbial identification[9]. These innovations in diagnostic methodologies signify a significant leap forward, enabling faster and more accurate identification of microbial involvement, ultimately contributing to improved patient outcomes.

16s rRNA Sequencing: Purpose: Identifying bacteria in culture-negative samples with clinical suspicion. Advantages: Higher culture rates compared to traditional methods, capable of detecting novel species.

Multiplex Respiratory Virus PCR: Current Utility: Rapid diagnosis of respiratory viruses within 24–48 hours. Impact: Expected decrease in PUO cases caused by respiratory virus infections due to swift diagnostic capabilities.

Vitamin B12 Deficiency

This etiology can often be missed and delay the diagnosis if not actively looked for in cases of pyrexia of unknown origin (PUO). The exact cause of pyrexia in megaloblastic anemia is not known but a proposed mechanism is that megaloblastic anemia leads to hyperplasia and thus increased activity within the bone marrow leading to systemic pyrexia[10]. Incidence of low-grade fever in nutritional megaloblastic anemia varies from 28% to 60%, literature search suggests that fever as a presenting symptom of vitamin B12 deficiency is rare. There are only a few case reports where vitamin B12 deficiency was solely attributed as the cause of pyrexia.

VII. Conclusion

In conclusion, the significance of clinical suspicion and the importance of maintaining an open-minded approach to diagnosis needs no further highlight. It is being repeatedly stressed that a single abnormal finding can be a valuable clue, and treatment based on clinical experience should be considered, with a positive therapeutic response aiding in narrowing down the diagnosis. The need to avoid rigidly sticking to previous diagnoses and the value of reevaluating patients, even if extensively assessed elsewhere has also been underscored. Additionally, the role of toxic vacuolization in WBCs as an indicator of sepsis and the potential benefits of using Penicillin G in antibiotic-resistant scenarios has been emphasized. Overall, the dynamic and evolving nature of medical diagnosis and the need for continuous reevaluation needs to be underscored.

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