

Approach to patients with Pyrexia of Unknown Origin Suspected to have Tuberculosis

MA Jalil Chowdhury

ABSTRACT

One of the most challenging problem a physician used to face in day to day practice is the evaluation of patients with prolonged pyrexia—a truly significant test of his clinical skills.

Causes of PUO vary according to geographical area, health care setup, investigations facilities, and physicians' attitude. Because of socioeconomic and other factors, infectious diseases are still very common in developing countries. Amongst the infectious causes tuberculosis usually extra pulmonary or miliary is the single most common infection in most PUO series.

Mycobacterium tuberculosis is a genius organism which can affect any and every organ system of the body. It can virtually produce any known clinical syndrome except true pregnancy. So it is reasonable to think of tuberculosis as a cause of fever in a PUO setting when no cause is obvious.

The most important investigation in a case of PUO is to evaluate the patient by a physician who has not seen the patient previously. The tests already done should be reviewed attentively. There might have some clue to diagnosis in those. Some investigations may have to be repeated; new investigations may have to be ordered. Definitive diagnosis of tuberculosis requires isolation of the tubercle bacillus from the body fluid or any tissue obtained by FNA or biopsy, which is often difficult. Institution of empirical anti tuberculous therapy may be justified in any patient of PUO where no specific diagnosis is evident after a reasonable diagnostic work-up and tuberculosis is a strong possibility and the patient is rapidly deteriorating.

"Humanity has three great enemies: fever, famine and wars. Of these by far the greatest, by far the most terrible is fever" – Sir William Osler (1849-1919). Terrible for the patient because of not curing within expected period and terrible for the physician for not reaching a diagnosis even after exhaustive investigation.

There are 3 types of fever usually the physicians encounter: acute onset fever usually producing no diagnostic or therapeutic problem; Recurrent fever; and third group having prolonged fever amongst which a group remains undiagnosed even after logical extensive investigations termed as pyrexia or fever of unknown or undetermined origin (PUO or FUO).

One of the most challenging problems a physician faces in his daily practice is the evaluation of a patient with prolonged pyrexia—a truly significant test of his clinical skills.

PYREXIA OF UNKNOWN ORIGIN

In 1961, Petersdorf and Beeson first defined PUO as "fever lasting for more than 3 weeks, more than 38.3°C on several occasions and no diagnosis after 1 week of indoor investigations".¹ Three weeks duration eliminated short lived infections; mainly viral fevers and 1 week of indoor investigations allow sufficient time for appropriate initial investigations to be completed.

Cost of hospitalization is increasing day by day. Now a days most of the patients of PUO can be managed as outdoor patients and incidence of HIV (human immunodeficiency virus), nosocomial infections and neutropenic patients are increasing day by day. Considering this, Durack and Street (1991) proposed a new classification of PUO (Table 1).² Major changes in new classification were that it didn't require 3 weeks duration to satisfy diagnosis of PUO and blood culture negative at 48 hours was a must.

WHEN A FEVER CASE DOES BECOMES PUO?

Unawareness of atypical presentations of common diseases (most important), lack of detailed initial clinical work up, delay in advising appropriate investigation, misinterpretation of either clinical feature or investigation result, false negative or positive test results and multiple pathologies in the same patient - are the few factors responsible for a fever case to be labeled as PUO. Repeated basic clinical evaluation is probably most important factor in reaching a diagnosis. But in some cases of PUO, the cause remains undiagnosed even after exhaustive investigations. Explanation for such fevers could be pathologies which are yet unidentified or diagnostic tests for them are not available widely or not advised.

Often a patient who complains of fever does not have fever when checked by thermometer. So 'I feel feverish, 'fever is inside the body...does not come in thermometer' should not be considered as PUO. According to one study (PUO of >1 year duration on average) 28% patients did not have fever when oral temperatures were taken for several weeks.³ They are the most anxious people and do doctor shopping. By this time they have done so many investigations failing to find any clue or solving their problem. They may be asked to record the temperature

Table 1: Classification of Fever of Unknown Origin (FUO)⁵

Category of FUO	Definition	Common etiologies
Classic	Classic Temperature >38.3°C (100.9°F) Duration of >3 weeks Evaluation of at least 3 outpatient visits or 3 days in hospital	Infection, malignancy, collagen vascular disease
Nosocomial	Temperature >38.3°C Patient hospitalized >24 hours but no fever on admission Evaluation of at least 3 days	<i>Clostridium difficile</i> enterocolitis, drug-induced, pulmonary embolism, septic thrombophlebitis, sinusitis
Immune deficient (neutropenic)	Temperature >38.3°C Neutrophil count < 500 per mm ³ Evaluation of at least 3 days	Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus
HIV-associated	Temperature >38.3°C Duration of > 4 weeks for outpatients, >3 days for inpatients HIV infection confirmed	Cytomegalovirus, <i>Mycobacterium avium-intracellulare</i> complex, <i>Pneumocystis carinii</i> pneumonia, drug-induced, Kaposi's sarcoma, lymphoma

HIV = human immunodeficiency virus.

Table 2: Common Etiologies of Fever of Unknown Origin⁵

Infections	Autoimmune conditions
Tuberculosis (especially extrapulmonary)	Systemic lupus erythematosus (SLE)
Endocarditis	Adult Still's disease
Abdominal abscesses	Polymyalgia rheumatica
Pelvic abscesses	Temporal arteritis
Dental abscesses	Rheumatoid arthritis
Osteomyelitis	Rheumatoid fever
Sinusitis	Inflammatory bowel disease
Cytomegalovirus	Reiter's syndrome
Epstein-Barr virus	Vasculitides
Human immunodeficiency virus	
Lyme disease	
Prostatitis	
Sinusitis	
Malignancies	Miscellaneous
Lymphoma	Drug-induced fever
Metastatic cancers	Complications from cirrhosis
Renal cell carcinoma	Hepatitis (alcoholic, granulomatous, or lupoid)
Colon carcinoma	Hepatic cirrhosis with active hepatocellular necrosis
Hepatoma	Deep venous thrombosis
Myelodysplastic syndromes	Sarcoidosis
Pancreatic carcinoma	Factitious fever
Chronic leukemia	
Sarcomas	
	Undiagnosed

daily consecutively for about two weeks before going for further evaluation.

CAUSES OF PUO

Causes vary according to geographical area, health care setup, investigations facilities, demographic pattern of population, and physicians' attitude for getting specific diagnosis. Infections (40%), neoplasms (20%), and collagen-vascular diseases (15%) are ultimately found responsible for the majority of the cases of PUO worldwide (The "Big Three"). Because of socioeconomic and other multiple factors, infectious diseases are still very common in developing countries. Amongst the infectious cause tuberculosis usually extra pulmonary or miliary is the single most common infection in most PUO series.⁴ Incidence of tuberculosis is many times higher in Indian subcontinent as compared to western countries (Table 2).

APPROACH TO PATIENTS WITH PUO

The first and foremost step is to establish that fever really exists. Patients should be instructed to measure oral temperature and record daily for at least two weeks. Detailed history and physical examination has probably not more significance in any other category of patients than PUO. Clinical evaluation should be repeated frequently. History should be re taken and patient should be re-examined by a physician who has not seen the patient previously. The investigations already done by the patient should be reviewed attentively.^{3,5} There might have some clue to diagnosis. Some investigations may have to be repeated; new investigations may have to be ordered. All medications should, if possible, be discontinued early in the evaluation to rule out a drug-induced fever. Persistence of fever beyond 72 hours after the suspected drug has been removed allows one to conclude that the drug is not the offending agent in producing the fever.⁶

APPROACH TO A PATIENT WITH PROLONGED PYREXIA WHEN TUBERCULOSIS IS SUSPECTED AS THE CAUSE

TB might have been missed at initial work up because of

- Failure to identify the findings correctly
- Not suspecting tuberculosis
- Delay in ordering appropriate tests
- Insufficient sample collection
- Difficulty in getting appropriate sample
- Not motivated for sending sample for mycobacterial staining, culture or PCR in addition to cytology and histopathology
- Pulmonary TB in AIDS is often subtle (normal chest x-rays in 15–30%)
- Misinterpretation of test result
- PPD is positive in < 50% of TB with PUO
- Less sensitivity of sputum smear microscopy

Why and when to suspect TB as PUO?

1. When no other cause found for fever
2. Organ based symptoms: there may not be any symptom other than fever
3. Organ based signs e.g., hepatomegaly
4. Past history of Tuberculosis
5. History of contact with smear positive TB patient
6. Lung infiltrates on previous chest x-ray; the subtle changes might have been missed in the past. Serial x-rays are essential tool
7. Clue in the investigations already done e.g., sterile pyuria.
8. Malnutrition
9. Immunosuppression
10. Diabetes, renal insufficiency or uremia/ dialysis, transplant
11. HIV
12. Drug abuser
13. Homelessness

Search for TB as a cause of PUO by organ based symptoms and signs and investigations

Mycobacterium tuberculosis is a genius organism which can affect any and every organ system of the body. It can virtually produce any known clinical syndrome except true pregnancy.

Miliary or chronic disseminated Tuberculosis

Splenomegaly may be found in miliary chronic disseminated tuberculosis. Choroid tubercle may be rarely found. MT is often negative. Miliary pulmonary lesions may not be obvious. It is to be noted that miliary pattern of chest x ray sometimes detected after meticulous

re-evaluation of the film only after the diagnosis is made by other means. Anemia and leukopenia may be present. A leukemoid response may indicate bone-marrow involvement and suggest diagnosis. Monocytosis may occur, but it is also found with other infections and neoplasia. Bone marrow biopsy may be diagnostic.^{7,8}

Pleural Tuberculosis

High ADA on the background of lymphocyte predominant exudative effusion is the diagnostic of tuberculosis. Pleural biopsy is sometimes helpful.

Cryptic Tuberculosis

Cryptic disseminated tuberculosis is an insidious form of presentation which mainly affects middle aged and elderly. Often the diagnosis is missed because possibility of tuberculosis is not considered. Lassitude, loss of weight, chronic ill health in the aged are erroneously attributed to some co-existent chronic disease or presumed occult tumors. Diagnosis is particularly difficult because choroidal tubercles are often absent, miliary pulmonary mottling may not be seen on chest radiography and the tuberculin test may be negative. The clinical features are often so non-specific that the diagnosis is frequently made only at autopsy.⁹

Splenic Tuberculosis

Isolated splenic tuberculosis is rare but can be a part of miliary tuberculosis. Abdominal ultrasonography revealing splenomegaly with multiple small hypo echoic lesions within the spleen can be anything from tuberculosis to abscess, lymphoma or carcinoma of spleen. Splenic puncture and biopsy can reveal the actual diagnosis.¹⁰⁻¹¹

Hepatic tuberculosis

Localized hepatic tuberculosis is rare; can be a part of disseminated miliary tuberculosis. There may be hepatomegaly. Sign symptoms are nonspecific. A moderate or marked increase in the serum levels of alkaline phosphatase, along with normal or mildly increased serum bilirubin, is considered suggestive of hepatic tuberculosis; however, these findings are not specific and may occur in other conditions, such as metastatic carcinoma, liver abscess, echinococcosis, amyloidosis, granulomatous diseases of varying etiologies, and active cirrhosis. Some authors suggest that, whenever there is a lack of etiological diagnosis of a granulomatous hepatitis, patients should be considered for an empirical trial with antituberculous drugs, especially if there is clinical deterioration, particularly in areas where tuberculosis is endemic.¹²⁻¹⁴ Liver biopsy points to the diagnosis. The specimen should be cultured for tubercle bacilli as well as examined histologically.

Gastrointestinal tuberculosis

Peritoneal biopsy: laparoscopic biopsy preferred to percutaneous biopsy. The role of ascitic fluid adenosine deaminase (ADA) in the diagnosis of TB peritonitis is unclear.¹⁵ The presence of an abnormal chest x-ray in a patient with ascites should alert one to the possibility of TB peritonitis.¹⁶ Colonoscopy with ileoscopy may be

Lymph node tuberculosis

Lymph node biopsy is the most frequent invasive test. If possible, anterior cervical, axillary, or inguinal node biopsy should be avoided because biopsies of these nodes are usually unhelpful/nondiagnostic and are often reported as "non specific inflammatory changes, cannot rule out infection/malignancy." More likely to be diagnostic are posterior cervical, supra/infraclavicular, or epitrochlear node biopsies.¹⁷⁻¹⁹ Hilar, mediastinal, or retroperitoneal node biopsies have a high diagnostic yield.²⁰ Certain characteristics like matted lymph node, calcification and preferential involvement of right paratracheal lymph node favors diagnosis of tuberculosis.

Psoas abscess

Patient may present with pain in the groin. MRI may or may not detect spinal tuberculosis; may be consequence of tuberculosis of the paravertebral glands.²¹

Pericardial tuberculosis

Pericarditis usually presents in three clinical forms, consisting of pericardial effusion, constrictive pericarditis and a combination of effusion and constriction.²²

The definite diagnosis of TB pericarditis is made by identification of mycobacterium TB in the pericardial fluid or tissue or the presence of caseous granulomas in the pericardium. Polymerase chain reaction (PCR) can identify DNA of mycobacterium TB from pericardial fluid. Pericardial biopsy provides a rapid and definite diagnosis but requires high technical skill and the yield from culture is low even with optimum specimen.^{2,6,12}

The Tygerberg²³ scoring system helps the clinician to decide whether pericarditis is due to TB or whether it is due to another cause : night sweats (1 point), weight loss (1 point), fever (2 points), blood leucocytes $< 10 \times 10^9/L$ (3points) serum globulin $>40g/L$ (3points). A total score of 6 or more is highly suggestive of TB pericarditis.¹³ In a developing nation such as ours, a high index of suspicion is required in all cases of prolonged fever and evidence of hemodynamic instability with high Tygerberg score. Echocardiography is indicated and finding of pericardial effusion with irregular border projecting into the effusion should suggest tuberculosis as the cause of the effusion. Anti tuberculous chemotherapy should be exhibited in such a patient and response to this treatment should therefore confirm the diagnosis. This is important because TB pericarditis is difficult to diagnose since definitive diagnosis requires culturing the TB bacilli from aspirated pericardial fluid or pericardial biopsy which requires technical skill and is often non diagnostic.

Renal tuberculosis

Microscopic hematuria may give clue to diagnosis. AFB can be found in urine sample collected over a period of 24 hours.²⁴

Adrenal tuberculosis

Rarely cause PUO, may be a part of chronic disseminated form of tuberculosis

Pott's disease

There may or may not be pain in the affected vertebra, commonly lower dorsal region. Care full examination may reveal gibbus. . Pott's disease can be missed in conventional X-ray. MRI and histopathological diagnosis are usually needed.

Mycobacterial culture and acid fast stain of specimens including sputum, urine, gastric juice, bone marrow aspirate, cerebrospinal fluid, pleural fluid, and pericardial fluid, paravertebral abscess, and lymph node aspirate are the main stay of diagnosis of tuberculosis in a patient with prolonged pyrexia.

NONSPECIFIC INVESTIGATIONAL HELP

Analysis of the previous films meticulously can reveal any subtle finding missed earlier.

ESR, CRP, IGRA are not of so much diagnostic. MT may be false positive in BCG vaccinated, asymptomatic infection with Mycobacterium tuberculosis or atypical mycobacteria. Serological tests (TB IgG, IgM, PCR blood) are not useful and are not recommended in many countries where false positive rates are expected to be high.

BAL can yield AFB when conventional sputum examination fails to diagnose tuberculosis.¹

Often in an appropriate clinical setting ADA in body fluids sometimes help to reach a diagnosis of tubercular origin.

Exploratory Laparotomy/laparoscopic examination: Before the era of laparoscopy and CT scan laparotomy used to consider for diagnosis of pyrexia of unknown origin when abdominal pathology was considered to be the cause.²⁵

Various nuclear scans e.g., PET (positron emission tomography) scan, indium 111 scan, radiolabelled leucocyte scan are done some times in work-up of PUO but they are not cost effective especially in developing countries.³

Positron emission tomography (PET) scan combined with computed tomography (CT) scan has been found to be helpful in diagnosis of extra pulmonary tuberculosis in patients with PUO.²⁶ PET/CT is helpful in identifying a site for biopsy. FDG PET scan can identify the hyper metabolic state in case of inflammation or tumor.²⁷

EMPIRICAL THERAPY IN PUO

Tuberculosis, particularly extra pulmonary tuberculosis, has emerged as the most common final diagnosis in patients presenting with FUO in most Indian studies. Sharma et al, in a combined prospective and retrospective study of 150 cases of FUO, found that infections, particularly tuberculosis, were the most common cause of FUO (50%).²⁸ Another group of investigators found tuberculosis as the cause of FUO in 26 of 121 patients (21.5%) in a prospective study. A recent study involving 60 patients with FUO who met the strict revised criteria established by Petersdorf found extra pulmonary tuberculosis to be the most common cause of FUO. All the patients tested

negative for human immunodeficiency virus (HIV). Extra pulmonary tuberculosis, particularly tuberculous mediastinal adenopathy, was the final diagnosis in 27 (45%) patients. Tuberculosis was the single most common in most PUO series.⁴

This strongly supports the view that the institution of empirical antituberculous therapy is justified in any patient of PUO where no specific diagnosis is evident after a reasonable diagnostic work-up.

But therapeutic trial with ethambutol and INH is not usually not practiced now a days because of fear of rapid development of resistance. If the patient is hemodynamically unstable and rapidly deteriorating e.g., in cryptic tuberculosis empirical antituberculous therapy may be rewarding. In the others temptation to start antituberculous therapy may be stopped till a reasonable diagnosis is reached. It is to be remembered that rifampicin has significant antimicrobial properties and many bacterial infections may respond partially to rifampicin.³

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