One of the most challenging problems a physician faces in practice is the evaluation of a patient with prolonged pyrexia - a truly significant test of his clinical skills. A thorough and detailed history with a good clinical examination and relevant investigations are necessary in every patient of prolonged pyrexia. It is important to remember that rarer manifestations of common diseases are more often seen than rare diseases.

“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).

In the 19th century, febrile illness caused more than 2/3rd of total deaths. Vaccination, vector control, better sanitation and advances in medical field have changed the scene significantly over last 100 years. Before 1960’s, there were no USG (ultrasonography), CT scan, C-ANCA (C - Anti neutrophilic cytoplasmic antibodies), PCR (polymerase chain reaction). It required blind multiple biopsies, exploratory laparotomy, therapeutic trials (with very few options) and even autopsy on several occasions for diagnosis, which is not the case today).

Fever: Definition and Concept
An oral morning temperature of more than 37.2° C (98.9° F) is defined as fever (Mackowiak 1992). Normally temperatures can vary up to 1° C in same person over a day. Older people have higher (by 0.5° C) temperature compared to young people. Rectal temperature is 0.5° C higher than oral temperature.

Axillary temperature is very unreliable. Whether fever by itself is harmful or body’s defense for a particular disease is a controversial subject. Fever increases survival in diseased animals (not consistently shown in humans). Growth and virulence of several bacterial species is impaired at high temperature (basis of malaria therapy in neurosyphilis) and temperature increases phagocytic and bactericidal activity of neutrophils and macrophages. Fever increases oxygen consumption (by 10-15% for each 1° C increase), increases caloric and uid requirement and can precipitate convulsions and heart failure in predisposed patients. Rigors are commonly seen in malaria, UTI (urinary tract infection), cholecystitis and sepsis.
Pyrexia of Unknown Origin
In 1961, Petersdorf and Beeson defined PUO as “Febrile illness lasting for more than 3 weeks, more than 38.3° C on several occasions and no diagnosis after 1 week of indoor investigations”. 3 weeks duration eliminated short lived infections, mainly viral fevers and 1 week of indoor investigations indicated that baseline investigations were normal.

Cost of hospitalization is increasing and most of the patients of PUO can be managed as outdoor patients and incidence of HIV (human immunodeficiency virus), nosocomial infections and neutropenic patients is increasing. Considering this, Durack and Street (1991) proposed a new classification of PUO (Table 1). 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 hrs was a must.

When Does a Fever Case becomes PUO?
Unawareness of atypical manifestations of common diseases (most important), lack of detailed bedside evaluation, delay in advising specific investigation, misinterpretation of either clinical feature or investigation result, false negative tests and multiple pathologies in the same patient - are the few factors. 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. Viral fevers, allergies, recently described genetic causes for recurrent fevers (like hyperimmunoglobulin D syndrome, mevalonate kinase deficiency) could be causes. Often a patient who complains of fever does not have fever when checked by thermometer. So ‘I feel feverish’, ‘fever is inside...does not come in thermometer’ should not be entertained. According to one study (PUO of >1 yr duration on average) 28% patients did not have fever when oral temperatures were taken for several weeks.

Causes of PUO
Causes will vary according to geographical area, health care setup (availability of investigations), demographic pattern of population, investigators attitude for getting specific diagnosis or early empirical therapy. Because of socioeconomic and other multiple factors, infectious diseases are still very common in developing countries. Incidence of tuberculosis is many times higher in India as compared to western countries. Some diseases like neoplasm and temporal arteritis occur more commonly in elderly. India has an average age pyramid with narrow top of aged people, which is in sharp contrast with developed nations, probably making such diseases relatively rare here (Table 2).
Pyrexia of Unknown Origin

Usually causes of PUO are divided into 5 categories: infections, malignancies, collagen vascular diseases, undiagnosed and miscellaneous.

More than 400 diseases have been documented to cause PUO. It is essential to know what contemporary common causes in India are. Table 3 gives a series of 83 patients with PUO (classical) from a multispecialty teaching hospital from Mumbai.

Approach of Patient with PUO

The first and foremost step is to establish that fever really exists. Strict oral temperature record must be kept. Detailed history and physical examination has probably not more significance in any other category of patients than PUO. Clinical evaluation should be repeated frequently and a thorough review of patients with already done investigations should be taken.

History

A detailed, careful, day by day history of symptoms, signs detected by previous physician - his notes, treatment given, response to treatment, all investigations and patient’s general condition in the context of his various daily activities must be enquired into.

Some guiding points for history of fever could be:

1. Since when
2. Onset - acute or gradual
3. Rigors, is it daily or on alternative days
4. Diurnal variation

<table>
<thead>
<tr>
<th>Table 2: Causes of PUO in USA, Europe and India*</th>
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<tr>
<td>All %</td>
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<tr>
<td>Infections</td>
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<td>Neoplasm</td>
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<td>No diagnosis</td>
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<td>Miscellaneous</td>
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(*Pooled data from various case series since 1960 are used.)

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<tr>
<th>Table 3: Cause of PUO in series of 83 patients (Ramamoorthy et al 2003, unpublished data)*</th>
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<tr>
<td>I. Tuberculosis 36.14%: Isolated mediastinal lymphadenopathy (6), meningitis (5), miliary (5), abdominal (4), lung abscess (1), pulmonary (1), MDR (multidrug resistant) - tuberculosis (1), disseminated TB (tuberculosis) (&gt; 2 noncontiguous areas involved) (4), spine (1), paraspinal and retropharyngeal abscess (1), tuberculoma brain (1).</td>
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<tr>
<td>2. Other infections 18.07%: Enteric fever (6), lung abscess (1), bacterial endocarditis (3), amoebic liver abscess (3), tropical pulmonary eosinophilia (4), streptococcal sepsis (source unknown) (4).</td>
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<tr>
<td>4. Neoplasm (3.61%): Ca (carcinoma) lung (1), Hodgkin’s disease, NHL (non Hodgkin’s lymphoma) of adrenal gland (1).</td>
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<td>6. No diagnosis 12.04%: 10 cases, 4 became afebrile in hospital, 4 within 3 weeks of discharge. 2 patients kept getting intermittent fever for 2 years, but were well otherwise and had resumed work. No patient with no diagnosis died in follow up of 2 years.</td>
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(*in () - number of cases are given)

Usually causes of PUO are divided into 5 categories: infections, malignancies, collagen vascular diseases, undiagnosed and miscellaneous.
5. Response to previous treatment
6. Associated symptoms

History of associated symptoms should be taken in same details for each symptom. Weakness, myalgia, headache, vague abdominal discomfort, burning of micturition (during fever) can be due to fever itself.

Interpretation of symptoms is very important and sometimes very difficult. Existing data shows that only about half patients with abdominal complaints and one fourth with CNS (central nervous system) symptoms had disease at the corresponding site.

Enquiry about anorexia and weight loss should be taken precisely. Absence of both makes any significant, progressive pathology unlikely. But not uncommonly thyroid disorders, diabetes mellitus, pheochromocytoma, malabsorption syndrome, lymphoma can present with increasing appetite and decreasing weight.

Past history of rheumatic fever, IV (intravenous) drug abuse, cardiac surgery (for bacterial endocarditis), contact with animals (psittacosis, brucellosis, cat scratch disease), high risk behaviour (HIV), smoking (Ca lung), cancer (for recurrence), diabetes mellitus (TB more common), immunosuppressant cytotoxic drugs (for neutropenic fevers), travel (Schistosomiasis), medications (almost any drug can cause drug fever - Digoxin in one of the few exceptions), immunization, allergen exposure or allergies and relevant family history should be obtained.

In nosocomial PUO - operations and procedures, devices should be considered as potential sites of infection. For neutropenic fevers - stage of chemotherapy, drugs administered, underlying disease status should be enquired into.

Physical Examination

Skin, nails, lymph nodes, fundi, oropharynx, lower limb deep veins, joints, spine, genitalia, wounds, drains should be examined. Signs may be very subtle and may require extraordinary efforts for their detection in PUO cases.

Tender lymph nodes, even if slightly enlarged (mononucleosis syndrome, Kikuchi disease), non-tender lymphadenopathy (TB, lymphoma, metastasis), vasculitic i.e. palpable and painful rash and oral ulcers (SLE and others), non-palpable purpura (thrombocytopenia), pitting nails (psoarisis), fundi (Roth’s spots, choroid tubercles), DVT (deep vein thrombosis) (recurrent pulmonary embolism), tender deformed spine (TB), genital ulcers (sexually transmitted infections, drug reactions), tender joints (RA), heart murmur on changing positions (myxoma), Osler’s nodes, Janeway’s lesions (endocarditis), tender liver (viral hepatitis, amoebic liver abscess), tender thyroid even if not enlarged (thyroiditis), evanescent salmon pink rash (Still’s disease), nasal polyps (Wegener’s granulomatosis), tender temporal artery (temporal arteritis), neck stiffness (meningitis), erythema nodosum (TB, sarcoidosis), lupus pernio (sarcoidosis), scars of herpes zoster (immunocompromised state), wide spread hyperpigmentation (Whipple’s disease) can help to narrow down differential diagnosis.

Investigations

By definition of PUO, baseline investigations i.e. CBC (complete blood count), ESR (erythrocyte sedimentation rate), LFT (liver function tests), RFT (renal function tests), CXR (chest X-ray), ECG (electrocardiogram), urine routine, sputum for AFB (acid fast bacillus) and blood cultures are non-conclusive. Repetition of some of these basic investigations like CXR and blood culture give positive result in significant number of patients.

Specific investigations - non-invasive (radiological, serological) and invasive (biopsies, uid aspirations) should be done taking clues from history, examinations and basic investigations. Non-invasive investigations should precede invasive, with possible exception of lumbar puncture.
Non-invasive tests are - USG abdomen, USG neck for lymph node, CT scan of chest and abdomen or other specific areas, 2D echo (two dimensional echocardiography), trans-esophageal echo, infectious disease serology like brucella, rickettsia, ANA (antinuclear antibodies) ds-DNA (double stranded deoxyribo nucleic acid), C-ANCA, P-ANCA (P - Antineutrophilic cytoplasmic antibodies), C3 (complement 3), C4 (complement 4) levels, ACE (angiotensin converting enzyme) levels, ferritin, thyroid function tests and tumor markers [like PSA (prostate specific antigen), CEA (carcino embryonic antigen)].

Invasive tests are - Lymph node excision biopsy, lumbar puncture, aspiration of pleural / ascitic / synovial uid, skin biopsy, liver biopsy, bone marrow biopsy and biopsy of a lesion shown on radiological investigation.

Before advising any test, stratify it’s present probability for given case. The desired speed of investigations in a particular case will vary according to hemodynamic status, progressing or regressing nature of disease and its magnitude, disease under consideration and type of PUO like neutropenic fevers which demands work-up in hours. In a critically ill patient, multiple investigations at same time can be justified but otherwise not (Table 4).

When no Clues at all!

Which investigation to take first and when to take next, while there is no clue at all for any specific disease is a crucial question. No further specific investigation and careful periodic follow up can be justified if patient is vitally stable, able to continue work, with normal appetite, without weight loss, normal ESR and showing improving trend. Such patients are sometimes called “benign” PUO. ESR alone should never be chased as investigations have shown normal people can have ESR > 100 / hr for years (Kyle, JAMA 1967, Wyler, South Med J 1977).

If at the end of such work up, no diagnosis becomes evident and patient shows deterioration, empirical therapy is the only option.

Periodic assessment of symptoms, signs and repeated basic investigations must be done. If any patient enters the category of benign PUO, further work up can be withheld and careful periodic follow up can be done.

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

PUO with No Diagnosis
This forms 10 - 20% of cases. Studies have shown no significant mortality in this group of patients even when followed up to 10 years. Recent studies have shown EBV (Epstein barr virus) and CMV infection can cause fever for more than 3 weeks in more than one third of adult patients (Arno, Lancet 1997). Such patients probably comprise the benign PUO.

Tuberculosis
Unequivocally is the commonest cause (even in developed countries in 21st century). Central hypodense areas (due to central necrosis) in the lymph nodes on CT scans is quite reliable sign and biopsy is not necessary always. Even at biopsy differentiation from sarcoidosis may be difficult. Serological tests (TB IgG, IgM, PCR blood) are not useful and are not recommended in India where false positive rates are unacceptably high. Empirical antituberculosis therapy (although not scientific) is a very common practice in a developing country like India.

Other Causes of PUO
Sarcoidosis, Kikuchi Fujimoto’s disease, recurrent pulmonary embolism, drug fever, adult onset Still’s disease, Wegener’s granulomatosis and factitious fevers are being increasingly recognized.

Dissecting aortic aneurysm, haemolytic anaemia, post myocardial infarction syndrome, cyclic neutropenia, temporal lobe epilepsy and familial Mediterranean fever are some of the rare causes.

Empirical Therapy in PUO
Usually not advisable. It should be considered only in haemodynamically unstable, rapidly deteriorating patients. Most of the patients give history of having had multiple antimicrobials which can cause negative blood cultures and partial response in TB (quinolones, macrolides). In presence of deteriorating constitutional symptoms compatible with TB, empirical AKT (anti Koch’s therapy) (anti tuberculosis therapy) should be instituted with careful follow up. Rifampicin has significant antimicrobial properties and many bacterial infections may respond partially. Very rarely metastasis with occult primary malignancy may call for empirical anti-cancer therapy if adequate characterization is possible on the basic of histopathology of metastatic lesion and/or results of marker studies.