Pyrexia of Unknown Origin (PUO)

Definition
Petersdorf and Beeson defined pyrexia of unknown origin (PUO) in 1961. It is defined as:

- A temperature greater than 38.3°C on several occasions.
- This should be accompanied by more than 3 weeks of illness.
- There should also be failure to reach a diagnosis, after 1 week of inpatient investigation.

This timing allowed exclusion of patients with protracted, but self-limited viral illnesses giving time for studies to be completed. This has now been modified to include patients who are diagnosed after 2 outpatient visits or 3 days in hospital.

Additional categories have now been added including:

- Nosocomial PUO in hospital patients with fever of 38.3°C on several occasions caused by a process not present or incubating on admission where initial cultures are negative and diagnosis unknown after 3 days investigation.
- Neutropenic PUO includes patients with fever as above with <1x 10^9 neutrophils with initial negative cultures and diagnosis uncertain after 3 days.\footnote{2}
- HIV-associated PUO includes HIV positive patients with fever as above for 4 weeks as outpatients or 3 days as inpatient, with an uncertain diagnosis after 3 days investigation where at least 2 days have been allowed for cultures to incubate.

Common causes of PUO\footnote{3}
Most cases are unusual presentations of common diseases e.g. tuberculosis, endocarditis, gallbladder disease and HIV infection, rather than rare or exotic diseases.\footnote{4}

- In adults: infections (40% of cases) and cancer (25% of cases) account for most of PUOs.\footnote{5} Autoimmune disorders account for 10-20% of cases.\footnote{4} Other (drugs, factitious etc)(10% of cases), Undiagnosed(10% of cases)
- Children: 30-50% of cases are due to infections, 5-10% cancer, autoimmune disorders 10-20%.
- If fever > 6 months 20% = infections, cancer or autoimmune. More important causes: Granulomatous diseases (Crohn’s disease, ulcerative colitis, sarcoidosis), factitious fever

Bacterial

- Abscesses
  - There may be no localising symptoms.
  - Previous abdominal or pelvic surgery, trauma or history of diverticulosis or peritonitis increase the likelihood of an occult intra-abdominal abscess.
  - Most commonly in the subphrenic space, liver, right lower quadrant, retroperitoneal space or the pelvis in women.
- Tuberculosis (TB)
  - Dissemination, which may occur in patients who are immunocompromised, makes initial presentation more constitutional symptoms than localising signs. Chest X-ray may be normal.
- Urinary tract infections (UTIs) are rare causes. Perinephric abscesses occasionally fail to communicate with the urinary system resulting in a normal urinalysis
• **Endocarditis** is a rare cause of PUO:
  o Culture-negative endocarditis is reported in 5-10% of endocarditis cases.
  o The HACEK group are responsible for 5-10% of cases of infective endocarditis and are the most common cause of Gram-negative endocarditis among people who do not abuse intravenous drugs.
  o This is a group of Gram-negative bacilli - *Haemophilus* spp. (*H. parainfluenzae*, *H. aphrophilus*, and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.
  o They are part of the normal oropharyngeal flora, are slow growers and prefer a carbon dioxide-enriched atmosphere.
  o Because of their fastidious growth requirements, they have been a frequent cause of culture-negative endocarditis.
  o Prior antibiotic therapy is the most frequent reason for negative blood cultures.
• **Hepatobiliary infections** e.g. *cholangitis* can occur without local signs and with only mildly elevated or normal liver function tests especially in the elderly.
• **Osteomyelitis** usually causes localised pain or discomfort at least sporadically.
• **Brucellosis** should be considered in patients with persistent fever and a history of contact with cattle, swine, goats or sheep, or patients who consume raw milk products.
• **Borrelia recurrentis** is transmitted by ticks. It is responsible for causing relapsing fever.
• Other spirochetal diseases that can cause PUO include *Spirillum minor* (Rat-bite fever), *Borrelia burgdorferi* (Lyme disease), and *Treponema pallidum* (syphilis).

**Viral**

• **Herpes viruses** such as *cytomegalovirus* and *Epstein-Barr virus* (EBV) can cause prolonged febrile illnesses with constitutional symptoms and no prominent organ manifestations, particularly in the elderly.
• **HIV:**
  o Prolonged febrile episodes are frequent in patients with advanced HIV infection.
  o Approximately 75% of the cases are infectious in nature, about 20-25% are due to lymphomas and a small fraction (0-5%) are due to HIV itself.
  o Over 80% of patients with AIDS and lymphomas have involvement of extranodal sites - usually the brain.

**Fungi**

• Immunosuppression, the use of broad-spectrum antibiotics, the presence of intravascular devices and total parenteral nutrition all predispose people to disseminated fungal infections.

**Parasites**

• **Toxoplasmosis**. This should be considered in patients who are febrile with lymph node enlargement.
• **Trypanosoma**, leishmania and amoeba species may rarely cause PUO.

**Rickettsial organisms**

• **Coxiella burnetii** may cause chronic infections, chronic Q fever or Q fever endocarditis may be identified in patients with a PUO.

**Psittacosis**
• Infection by the causative organism, *Chlamydophila* should be considered in a patient with PUO who has a history of contact with birds.

**Lymphogranuloma venereum**

• This should also be considered, but is rare.

**Neoplasms**

• Hodgkin and non-Hodgkin lymphomas may cause PUO.
• Leukaemias may also be responsible.
• Among solid tumors, *renal cell carcinoma* is most commonly associated with PUO.
• Solid tumors such as *adenocarcinomas of the breast, liver, colon or pancreas and liver metastases* from any primary site may present with fever.
• Malignant *histiocytosis* is a rare rapidly progressive malignant disease.
• Atrial myxoma

**Drug fever**

A wide variety of drugs can cause drug fever:

• The most common are beta-lactam antibiotics, procainamide (now discontinued) and isoniazid. Stopping the drug generally leads to recovery within 2 days.
• It is usually accompanied by a rash.
• Antimicrobials
• Antihistamines
• Antiepileptics – Barbiturates, Phenytoin
• NSAIDs
• Antihypertensives - Hydralazine, methyldopa

**Collagen vascular and autoimmune diseases**

• Systemic-onset *juvenile rheumatoid arthritis*. High-spiking fevers, non-pruritic rashes, arthralgias and myalgias, pharyngitis and lymphadenopathy typically are present.

• *Polyarteritis nodosa* (PAN), *rheumatoid arthritis* and mixed connective-tissue diseases should be considered.
• *Still's disease*
• *SLE*

**Granulomatous diseases**

• *Sarcoidosis*
• *Crohn's disease* (most common gastro-intestinal cause)
• *Granulomatous hepatitis*

**Vasculitides**

• *Giant cell arteritis* and also the related *polymyalgia rheumatica†*
• Polyarteritis nodosa
• *Behcet's* has also been reported*
Peripheral pulmonary emboli
Peripheral pulmonary emboli and occult thrombophlebitis can cause PUO.

Inherited diseases
Familial mediterranean fever

Hyperthyroidism and subacute thyroiditis

- These are the most common endocrine causes of PUO.
- Adrenal insufficiency is a rare, but potentially fatal cause of PUO.

Miscellaneous

- Endocrine - Adrenal insuffic, Phaeocromocytoma
- Respiratory - PE, Sarcoidosis
- Alcoholic hepatitis
- Factitious fever

Kikuchi disease
Kikuchi disease is a self-limiting necrotizing lymphadenitis. It has been reported as a cause of PUO.\(^9\)

Undiagnosed
10-15% of patients remain undiagnosed despite extensive investigations and in 75% of these the fever resolves spontaneously. In the remainder, other signs and symptoms make the diagnosis clear.

Epidemiology

Incidence
This is a common problem.

- In patients older than 50 years more than 30% of cases are related to connective-tissue disorders and vasculitic disorders.
- Giant cell arteritis and polymyalgia rheumatica account for 50% of the cases.

Diagnosis
The first step is to confirm temperature by taking it yourself. Look for signs usually accompanying fever e.g. tachycardia, chills.

It is very important to take a thorough history:\(^10\)

- Inquire about symptoms from all major systems. Include general complaints e.g. fever, weight loss, night sweats, headaches and rashes.
- Record all complaints even if not currently present. Previous illnesses including surgery and psychiatric problems are important.
- Discuss nutrition including consumption of dairy products and source of these products.
- Drug history should be recorded, to include over-the-counter medications, prescription medications and any illicit substances.
- Immunization status should be documented.
- Enquire about family history of illness.
• Occupational history should include exposure to chemicals/animals.
• Take a history of travel and recreational habits - including possible exposure to ticks and other vectors.
• Sexual history should be recorded.

Examination of the patient should include:

• Documentation of fever and exclusion of factitious fever (may be up to 10% of cases) are essential early steps in the physical examination.
• Measure the fever more than once and in the presence of another. Electronic thermometers give access to rapid and unequivocal documentation of fever.
• Diseases such as brucellosis, borreliosis and Hodgkin disease tend to cause recurrent episodes of fever.
• Physical examination should be repeated daily while the patient is in hospital. Particularly watch for:
  o Rashes
  o Lymph node enlargement
  o Signs of arthritis
  o New/changing cardiac murmurs
  o Abdominal tenderness or rigidity
  o Fundoscopic changes and neurological deficits
• The pattern of fever is usually of little help in the diagnosis. Correlation between fever patterns and specific diseases is weak. The exception is in tertian and quartan malaria, where the diagnosis is usually made within 3 weeks.

Investigations
Approach to PUO

4 stages of assessment

Stage 1: Hx & Ex & Preliminary Ix.

Stage 2: Review Hx & Repeat Ex, Specific Ix

Stage 3: Invasive Ix

Stage 4: Therapeutic trial

Stage 1


Preliminary investigations: WBC and differential count, MSU, Blood cultures x 3, ESR/CRP, CXR, Thick and thin films, Mantoux test
Stage 2 Ix

- ASO streptococcal disease
- Hepatitis serology
- HIV
- VDRL/TPHA
- Mantoux
- Viral screen - CMV, EBV
- Atypical pneumonia
- Legionnaires
- Mycoplasma
- Psittacosis
- Q fever
- Brucella
- Lyme serology
- LDH
- Rheumatoid factor
- Autoantibodies
- CPK
- SPEP/UPEP

Stage 3 (invasive Ix)

- Review the patient's history and examination yet again
- Ultrasound scan
- CT TAP/ MRI
- ECHO
- Bone marrow aspirate, Tissue / liver / lymph node /temporal art Bx
- Lumbar puncture
- Nuclear medicine - bone /WCC scan
- PET

Stage 4

- Clinically challenging - get expert help! Clinical balance between trial antimicrobial (often anti tuberculosis regimen) or corticosteroid trial.

Management

This will depend on diagnosis. Empirical treatment has never been advocated in cases of PUO. There are, however, three important exceptions:

- Cases that meet criteria for culture-negative endocarditis
- Cases suggestive of cryptic disseminated tuberculosis (or other granulomatous infections)
- Cases in which temporal arteritis (with vision loss) is suspected

In immunocompromised host

Any course of management should include consideration of risk-benefit for the patient. The patient may be clinically well, apart from fever, but broad-spectrum treatment may bring debilitating side-
Disease course can be rapid, progressive and life threatening.

- In neutropenic patients fever may be first and only sign of bacteraemia:
  - Gram-negative organisms were mainly responsible in the past, but now Gram-positive ones are most common isolates in many units, especially coagulase-negative staphylococci. However, 50-60% of cultures will be negative despite rigorous investigations and empirical treatment is required.
  - In high swinging fever without any obvious focused or positive cultures, deep fungal infection is likely and in fever persisting for > 72 hours should add amphotericin B. This preparation has high levels of toxicity and alternatives have been trialled and found equivalent in efficacy, but with reduced toxic side-effects. In cancer patients with neutropenia, amphotericin B is the only anti-fungal for which there is evidence suggesting that it might reduce mortality.
- Take cultures and institute immediate antibiotic therapy before waiting for results:
  - Commonly used regimens include anti-pseudomonal penicillin plus aminoglycoside e.g. piperacillin/gentamicin; 3rd generation cephalosporin e.g. ceftazidime or meropenem.
  - These are very effective against common Gram-negative organisms, but less so against Gram-positive ones which are now a more common problem. Reliably effective antibiotic against these are glycopeptides e.g. vancomycin. These are not generally added to empirical treatment because of their toxicity, cost and fact that coagulase-negative staphylococci rarely cause death.
  - Generally vancomycin should be only used when blood culture results are known. 4th-generation cephalosporin e.g. cefepime which include Gram-positive bacteria in their spectrum are under investigation.
- If patient responds to initial treatment, continue for at least 7 days and ideally until neutrophil count reaches >0.5x 10^9/l. If not the therapy should be changed.

In non-neutropenic immunosuppressed patients, the situation is rarely immediately life threatening and the diagnosis should be pursued as above.

**Document references**

3. Chan-Tack KM; Common causes of PUO. eMedicine, March 2006.


