

# Pyrexia of unknown origin

## Definition

Petersdorf and Beeson defined pyrexia of unknown origin (PUO) in 1961<sup>[1]</sup>. It is defined as:

- A temperature greater than 38.3°C on several occasions.
- Accompanied by more than three weeks of illness.
- Failure to reach a diagnosis after one 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 two outpatient visits or three days in hospital.

The term 'fever of unknown origin' (FUO) is also sometimes used. PUO and FUO are used interchangeably in the scientific literature. PUO is used throughout this article for the sake of consistency.

Additional categories were introduced in 1991, including<sup>[2]</sup>:

- 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 three days of investigation.
- Neutropenic PUO, which includes patients with fever as above with  $<1 \times 10^9$  neutrophils, with initial negative cultures and diagnosis uncertain after three days.
- HIV-associated PUO, which includes HIV-positive patients with fever as above for four weeks as outpatients or three days as inpatients, with an uncertain diagnosis after three days of investigation, where at least two days have been allowed for cultures to incubate.

# Common causes of pyrexia of unknown origin<sup>[3]</sup> <sup>[4]</sup>

Most cases are unusual presentations of common diseases – eg, [tuberculosis](#), [endocarditis](#), [gallbladder disease](#) and [HIV infection](#), rather than rare or exotic diseases.

- In adults, infections and cancer (25–40% of cases each) account for most PUOs<sup>[5]</sup>. Autoimmune disorders account for 10–20% of cases.
- In children, infectious disease (37.6%) is the main cause of PUO, followed by malignancy (17.2%), miscellaneous disease (16.1%) and collagen vascular disease (14.0%).

## Healthcare-related PUO

Common causes include medication-induced fever, postoperative complications (eg, occult abscesses), septic thrombophlebitis, recurrent pulmonary emboli, myocardial infarction/Dressler's syndrome, stroke, blood transfusion reactions, and *Clostridium difficile* colitis.

## Bacterial

- Abscesses:
  - There may be no localising symptoms.
  - Previous abdominal or pelvic surgery, trauma or history of diverticulosis or peritonitis increases the likelihood of an occult [intra-abdominal abscess](#).
  - They are most commonly in the subphrenic space, liver, right lower quadrant, retroperitoneal space or the [pelvis in women](#).
- [Tuberculosis](#) – when dissemination has occurred (eg, in patients who are immunocompromised) the initial presentation is more likely to consist of constitutional symptoms than localising signs. CXR may be normal.
- [Urinary tract infections \(UTIs\)](#) – these are rare causes. Perinephric abscesses occasionally fail to communicate with the urinary system, resulting in a normal urinalysis.

- Endocarditis (this is a rare cause of PUO):
  - Culture-negative endocarditis is reported in 5-10% of endocarditis cases.
  - The HACEK group is responsible for 5-10% of cases of **infective endocarditis** and is the most common cause of Gram-negative endocarditis among people who do not abuse intravenous drugs:
    - 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.
    - They are part of the normal oropharyngeal flora, are slow growers and prefer a carbon dioxide-enriched atmosphere.
    - Because of their fastidious growth requirements, they have been a frequent cause of culture-negative endocarditis.
  - Previous antibiotic therapy is the most frequent reason for negative blood cultures.
- Hepatobiliary infections (eg, **cholangitis**) - these can occur without local signs and with only mildly elevated or normal LFTs, especially in the elderly.
- **Osteomyelitis** - this usually causes localised pain or discomfort at least sporadically.
- **Brucellosis** - this should be considered in patients with persistent fever and a history of contact with cattle, swine, goats or sheep, or in patients who consume raw milk products.
- *Borrelia recurrentis* - this is transmitted by ticks. It is responsible for causing **relapsing fever**.
- Other spirochetal diseases that can cause PUO - these include *Spirillum minor* (**rat-bite fever**), *Borrelia burgdorferi* (**Lyme disease**) and *Treponema pallidum* (**syphilis**).

## Viral

- **Herpes viruses** (such as **cytomegalovirus (CMV)** and **Epstein-Barr virus (EBV)**) - these can cause prolonged febrile illnesses with constitutional symptoms and no prominent organ manifestations, particularly in the elderly.
- **HIV**<sup>[6]</sup>:
  - Prolonged febrile episodes are frequent in patients with advanced HIV infection.
  - The majority of the cases are infectious in nature. The remainder of them are mainly due to lymphomas, and a small fraction of them are due to HIV itself.
  - Patients with **AIDS** and lymphoma often have extranodal involvement, particularly CNS, gastrointestinal tract, liver and bone marrow.
  - A patient with a low CD4 count who presents with progressive dyspnoea, a nonproductive cough, and hypoxia should have evaluation for pneumocystis pneumonia (PCP). A patient with fever, loose stools, abdominal pain, and recent antimicrobial therapy should be assessed for *C. difficile* colitis.
  - If not infective, then consider malignancy, medication reactions (eg, to antiretrovirals) and autoimmune conditions (uncommon in HIV).

## 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 - these may rarely cause PUO.
- **Malaria** is the most common cause of fever in the returning traveller.

## 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, [Chlamydia psittaci](#) should be considered in a patient with PUO who has a history of contact with birds.

## Lymphogranuloma venereum<sup>[7]</sup>

This should also be considered but is rare.

## Neoplasms

- [Hodgkin's lymphoma](#) and [non-Hodgkin's lymphoma](#) - these may cause PUO.
- Leukaemias - these may also be responsible.
- Among solid tumours - [renal cell carcinoma](#) is most commonly associated with PUO.
- Solid tumours (such as adenocarcinomas of the breast, liver, colon or pancreas) and liver metastases from any primary site - these may present with fever.
- [Malignant histiocytosis](#) - this is a rare, rapidly progressive malignant disease.

## Drug fever<sup>[8]</sup>

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 two days.
- It is usually accompanied by a rash.

## Collagen vascular and autoimmune diseases

- Systemic-onset [juvenile idiopathic 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.

### **Granulomatous diseases**

- Sarcoidosis.
- Crohn's disease (the most common gastrointestinal cause).
- Granulomatous hepatitis.

### **Vasculitides**

- Giant cell arteritis and also the related polymyalgia rheumatica.
- Polyarteritis nodosa.
- Behçet's disease.

### **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.

### **Kikuchi's disease**

Kikuchi's disease is a self-limiting necrotising lymphadenitis. It has been reported as a cause of PUO.

### **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

This is a common problem. In western countries, connective tissue diseases, [vasculitis](#) syndromes and granulomatous diseases are the most common non-infectious causes. Among these conditions, [giant cell arteritis](#) and [polymyalgia rheumatica](#) are the most frequent specific diagnosis in the elderly. In younger patients, the most frequent diagnosis is adult-onset Still's disease.

## Diagnosis<sup>[3]</sup> <sup>[4]</sup>

The first step is to confirm temperature by taking it yourself. Look for signs usually accompanying fever – eg, tachycardia, chills. It is very important to take a thorough history:

- Inquire about symptoms from all major systems. Include general complaints – eg, 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 the source of these products.
- Drug history should be recorded, to include over-the-counter medications, prescription medications and any illicit substances.
- Immunisation 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

This should include:

- Documentation of fever and exclusion of factitious fever (may be up to 10% of cases), which are essential early steps in the physical examination.
- Measuring 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](#), [Lyme borreliosis](#) and [Hodgkin's disease](#) tend to cause recurrent episodes of fever.
- Physical examination should be repeated daily while the patient is in hospital. Particularly, watch for:
  - Rashes.
  - Lymph node enlargement.
  - Signs of arthritis.
  - New/changing cardiac murmurs.
  - Abdominal tenderness or rigidity.
  - 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 three weeks.

## Investigations<sup>[3]</sup> <sup>[4]</sup>

- FBC, erythrocyte sedimentation rate (ESR), U&Es, C-reactive protein (CRP), LFTs, antinuclear antibody (ANA), Rh factor and TFTs should be taken.
- Labelled white cell scan; in this investigation white cells are labelled extracorporeally and then re-injected into the patient. It is used to identify areas of sepsis. If the patient is neutropenic then donor white cells may be used. False positive scans may occur with haematomas and inflammatory disease. False negatives may occur in chronic sepsis.



- Blood cultures (preferably having been off antibiotics for several days) should be taken at differing times and from different sites. Culture for two weeks to detect slow-growing organisms and on special media if necessary.
- Culture urine, sputum, stool, CSF and morning gastric aspirates (if tuberculosis is suspected).
- CXR, abdominal CT scan and echocardiography (if endocarditis or atrial myxoma is suspected) should be considered.
- CT, intravenous pyelogram (IVP), MRI and positron emission tomography (PET) scanning all have a place in diagnosis.
- Hybrid fluorodeoxyglucose (18 F) (FDG-PET)/CT is a technique with high sensitivity and a relative non-specificity for malignancy, infection and inflammation<sup>[5]</sup>. This makes it an ideal diagnostic tool for the investigation of PUO. It should preferably be used in the early work-up of a patient, to guide more focused investigations. The possibility of false positives should, however, be kept in mind.
- Invasive procedures for abnormal findings:
  - Lumbar puncture for headache.
  - Skin biopsy for rash.
  - Lymph aspiration or biopsy for lymphadenopathy.
  - In an HIV-positive patient - bone marrow aspiration or biopsy.
  - Abnormal LFTs should prompt a liver biopsy (even if normal size).
  - Laparoscopy or laparotomy is rarely necessary in the light of modern diagnostic techniques but may be required in patients who are deteriorating.
- Therapeutic trials if a diagnosis is strongly suspected - eg, tuberculosis, brucellosis.

# Management

This will depend on diagnosis. A fundamental principle in the management of FUO is that empirical antimicrobial therapy should be withheld whenever possible in a stable non-neutropenic or immunocompromised and/or non-critically ill patient until the cause of the fever has been determined so that that treatment can be tailored to a specific diagnosis. This approach is based on the observation that nonspecific treatment rarely cures PUO and has the potential to delay reaching the correct diagnosis<sup>[9]</sup>. There are, however, three important exceptions to the rule:

- 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 an immunocompromised host

Any course of management should include consideration of risk:benefit for the patient. The patient may be clinically well apart from fever; however, broad-spectrum treatment may bring debilitating side-effects.

### PUO in HIV-infected patients

Most are the result of opportunistic infections among patients not on antiretroviral therapy (ART) or with a suppressed viral load. Their prevalence changes by geographic location of the patient<sup>[10]</sup>. 18F FDG-PET/CT identified the cause of PUO in 85% patients with HIV in one study<sup>[11]</sup>. The causes included tuberculosis (n = 8), lymphoma (n = 3), non-tuberculous mycobacteria (n = 3), pneumococcal infection (n = 1), visceral disseminated leishmaniasis (n = 1), and dental infection (n = 1). The remaining 3 patients had drug-induced or HIV-related fever.

### Neutropenic patients

This is also discussed in the separate [Neutropenic Patients and Neutropenic Regimes](#) article. The disease course can be rapid, progressive and life-threatening:

- In **neutropenic patients**, fever may be the 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, about 70% of cultures will be negative despite rigorous investigations, and empirical treatment is required.
  - In high swinging fever without any obvious focus or positive cultures, deep fungal infection is likely and, in fever persisting for >72 hours, an antifungal should be added. For many years, amphotericin was the gold standard. However, better tolerated (but more expensive) options are now available, including fluconazole, itraconazole and posaconazole. Amphotericin is recommended as an empirical antifungal treatment for patients with prolonged neutropenia.
- Take cultures and institute immediate antibiotic therapy before waiting for results:
  - Commonly used regimens include antipseudomonal penicillin plus aminoglycoside - eg, piperacillin/gentamicin; third-generation cephalosporin - eg, 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 antibiotics against these are glycopeptides - eg, vancomycin. These are not generally added to empirical treatment because of their toxicity and cost and the fact that coagulase-negative staphylococci rarely cause death.
  - Generally, vancomycin should be used only when blood culture results are known. Newer options have been developed but despite greater cure rates, they have not been shown to be more effective in reducing mortality.
- If a patient responds to initial treatment, continue for at least seven days and ideally until the neutrophil count reaches  $>0.5 \times 10^9/L$ . 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.

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## Further reading

- [Fever in under 5s: assessment and initial management](#); NICE Guidance (last updated November 2021)
- [Brown I, Finnigan NA](#); Fever of Unknown Origin.

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