Fever

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Abstract

Fever is an elevation of body temperature mediated by the hypothalamus in response to exogenous pyrogens and pyrogenic cytokines. Patients with acute fever should be assessed promptly for signs of sepsis. Pyrexia of unknown origin (PUO) is defined as a fever $\geq$38.3 °C on several occasions over a period of at least 3 weeks, with uncertain diagnosis after a number of obligatory tests. A diagnostic algorithm is outlined in which the most important steps are a thorough history and physical examination, with investigations in a search for potentially diagnostic clues. Scintigraphic methods, such as ^{67}gallium citrate, labelled leucocytes and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), are often used in PUO. The favourable characteristics of FDG-PET/computed tomography mean that conventional scintigraphic techniques are being increasingly replaced by this technique where PET is available. Most patients with undiagnosed PUO have benign self-limiting or recurrent fever.

Keywords Diagnostic algorithm; fever; periodic fever; pyrexia of unknown origin

Key points

- Patients with acute fever should be evaluated for signs of sepsis because they require prompt medical attention
- The key to diagnosis of a pyrexia of unknown origin (PUO) is thorough and repeated history-taking and clinical examination, combined with baseline investigations to elicit potential diagnostic clues
- In all patients with PUO, factitious fever and drug fever should be considered and ruled out early in the diagnostic process
- In cases of PUO, conventional scintigraphic techniques should be replaced by FDG-PET/CT in institutions where it is available
- Because many patients with undiagnosed PUO have benign self-limiting or recurrent fever, therapeutic trials with antibiotics, corticosteroids or antituberculosis agents should be avoided, except in patients whose condition is deteriorating

Patients presenting with fever

Normal body temperature is ordinarily maintained by the thermoregulatory centre of the hypothalamus despite the effects of environmental changes. Fever is an elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in the hypothalamic set point. Pyrogens are substances that cause fever. Examples of exogenous pyrogens are microbial products, including toxins and whole microorganisms. The classic example of an exogenous pyrogen is the lipopolysaccharide (endotoxin) produced by all Gram-negative bacteria. Pyrogenic products of Gram-positive organisms include the enterotoxins of *Staphylococcus aureus* and the group A and B streptococcal toxins. Pyrogenic cytokines (e.g. interleukin-1, interleukin-6, tumour necrosis factor) can also be induced by a range of pathogens as well as by inflammatory processes, tissue necrosis or immune complexes.

Once the hypothalamic set point has been raised, temperature increases for several reasons. Neurones in the vasomotor centre are activated and vasoconstriction commences, decreasing heat loss from the skin. Shivering increases heat production from the muscles. Non-shivering heat production from the liver also contributes to increasing core temperature. In humans, behavioural adjustments (e.g. putting on more clothing) raise body temperature by decreasing heat loss. The processes of heat conservation and heat production continue until the temperature of the blood surrounding the hypothalamic neurones matches the new thermostat setting.

Distinction must be made between fever and hyperthermia. Hyperthermia, in which the hypothalamic set point is unchanged, is characterized by an uncontrolled increase in body temperature that exceeds the body's ability to lose heat. In contrast to fever in infections, hyperthermia does not involve pyrogenic molecules and does not respond to antipyretics.

Management of patients with acute fever

First, the patient should be evaluated for signs of sepsis requiring prompt medical attention. Sepsis was previously characterized using systemic inflammatory response syndrome criteria, but is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in the total Sequential Organ Failure Assessment score of $\geq$2 as a result of infection (see *Medicine* 2013; **41**(11): 667–669).

In a case of possible sepsis, a full history and physical examination should be performed, after resuscitation if needed, followed by laboratory tests (haemoglobin, platelet count, leucocyte and differential count, serum C-reactive protein (CRP), electrolytes and creatinine, urinalysis), two blood cultures, a urine culture, sputum culture if possible and a chest X-ray.

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Empirical antibiotic therapy should be instituted within 1 hour, according to local antibiotic prescribing policies.

A history should include travel, occupation and leisure pursuits, sexual history, illicit parenteral drug use, animal contact and previous drug therapy; this together with physical examination findings, should guide further management. In all patients with nuchal rigidity, a lumbar puncture should be performed (total and differential leucocyte count, protein concentration, cerebrospinal fluid:blood glucose ratio, Gram stain and culture) as soon as possible. A lumbar puncture should be considered in patients with otherwise unexplained fever who are suffering from a headache, photophobia, altered mental status or other neurological symptoms. Fever in the returning traveller requires further detailed assessment (see *Medicine* 2014; **42**(2): 66–72), recognizing that conditions such as falciparum malaria can rapidly be lethal and require urgent diagnosis and treatment.

Pyrexia of unknown origin (PUO)

In 1961, PUO was originally defined by Petersdorf and Beeson as an illness of >3 weeks' duration, fever ≥38.3 °C (101 °F) on several occasions and diagnosis uncertain after 1 week of study in hospital. This definition has been modified, removing the requirement that the evaluation must take place in the hospital and refined to include four different subgroups – classical, nosocomial, neutropenic and human immunodeficiency virus (HIV)-related – each requiring different investigative strategies.

For classical PUO, the quantitative criterion (diagnosis uncertain after 1 week of study in hospital) has been changed to a qualitative criterion that requires a list of certain investigations to be performed to reduce selection bias. Defining the initial investigations remains a matter of debate, but it is generally agreed that the initial diagnostic protocol required for a case to qualify as PUO should include at least the following: a comprehensive history and physical examination, routine blood tests, antinuclear antibodies, rheumatoid factor, microscopic urinalysis, three blood cultures, a urine culture and other cultures if clinically indicated, chest X-ray, abdominal ultrasonography and a tuberculin skin test or interferon-γ release

Definition of PUO

- Fever ≥38.3 °C (101 °F) on three occasions
- >3 weeks' duration
- Exclusion of immunocompromised patients: neutropenia (leucocyte count $<1.0 \times 10^9$/litre and/or granulocyte count $<0.5 \times 10^9$/litre) during at least 1 week within the 3 months preceding the fever, known HIV infection, known hypogammaglobulinaemia (IgG <50% of normal value), use of the equivalent of >10 mg prednisone during at least 2 weeks in the previous 3 months
- Diagnosis uncertain after thorough history-taking, physical examination and the following obligatory investigations: ESR or CRP, haemoglobin, platelet count, leucocyte and differential count, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, serum transaminases, lactate dehydrogenase, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures ($n = 3$), urine culture, chest X-ray, abdominal ultrasonography and tuberculin skin test or IGRA, HIV test

ESR, erythrocyte sedimentation rate.

Table 1

Common causes of classical PUO

Infections	
Bacterial	Infective endocarditis, abdominal abscesses, diverticulitis, renal abscess, lung abscess, prostatitis, sinusitis, infected vascular catheter, septic arthritis and osteomyelitis, spondylodiscitis and epidural abscess, infected joint/vascular prosthesis, dental infection, brucellosis, Q fever, rickettsiosis, tuberculosis, enteric fevers
Viral	Cytomegalovirus, Coxsackie virus, Epstein–Barr virus, hepatitis A, B, C or E, HIV, parvovirus
Fungal	Endemic mycosis, aspergillosis, candidiasis, cryptococcosis, histoplasmosis
Parasitic	Malaria, leishmaniasis
Non-infectious inflammatory disorders	
Systemic rheumatic diseases	Ankylosing spondylitis, Behçet's disease, cryoglobulinaemia, dermatomyositis, Felty's syndrome, gout/pseudogout, mixed connective tissue disease, polymyositis, reactive arthritis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome
Vasculitis	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), giant cell vasculitis/polymyalgia rheumatica, granulomatosis with polyangiitis (Wegener's granulomatosis), polyarteritis nodosa, Takayasu's arteritis
Autoinflammatory disorders	Adult-onset Still's disease, familial Mediterranean fever
Granulomatous diseases	Sarcoidosis
Neoplasia	
Haematological	Lymphoma, leukaemia, multiple myeloma, myelodysplastic syndrome, myelofibrosis
Solid tumours	Most solid tumours and metastases can cause fever; the most common causes of PUO are breast carcinoma, colon carcinoma, hepatocellular carcinoma, lung carcinoma, pancreatic carcinoma and renal cell carcinoma
Miscellaneous	Adrenal insufficiency, amyloidosis, atrial myxoma, autoimmune haemolytic anaemia, autoimmune hepatitis, Castleman's disease, drug fever, factitious fever, inflammatory bowel disease, haemophagocytic syndrome, hyperthyroidism, Kawasaki's syndrome, phaeochromocytoma, pulmonary embolism/thrombosis

Table 2