Fever

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Abstract

Fever is an elevation of body temperature mediated by the hypothalamus, as a result of prostaglandin E_2 synthesis-induced 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 higher than 38.3°C on several occasions during 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 thorough history and physical examination, with investigations in a search for potentially diagnostic clues (PDCs). 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/CT mean that conventional scintigraphic techniques are 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

The patient 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 the 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 or 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. Sundry bacterial and fungal products induce the synthesis and release of pyrogenic cytokines (endogenous pyrogens, such as interleukin-1, interleukin-6, tumour necrosis factor, and interferon α), as do viruses. Inflammatory processes, tissue necrosis or immune complexes can also induce the production of pyrogenic cytokines. Current concepts suggest that pyrogenic cytokines entering the systemic circulation induce the synthesis of prostaglandin E_2 (PGE_2), which accounts for the non-specific myalgias and arthralgias. Some systemic PGE_2 escapes destruction by the lung and accesses the hypothalamus via the internal carotid artery. The elevation of PGE_2 in the brain raises the hypothalamic set point for core temperature.

Once the hypothalamic set point is 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. Hyperthermia can be rapidly fatal because of a lack of a thermal ceiling. Hyperthermia characteristically does not respond to antipyretics. In fact, peripheral PGE_2 production is a potent immunosuppressant.

Fever patterns

Characteristic fever patterns are well reported but in most cases are more historically interesting than clinically useful. However, they can provide clues to diagnoses, such as brucellosis with its undulant fever pattern, compared to the step-wise increasing and remitting fever of typhoid. The Pel–Ebstein pattern of fever lasting 3–10 days followed by afebrile periods of 3–10 days can be classic for Hodgkin's disease and other malignant lymphomas but is uncommon.

Relative bradycardia occurs in infections caused by facultative intracellular microorganisms such as *Salmonella* and brucellosis, infections associated with increased intracranial pressure, some drug-induced fevers, and factitious fever. In newborns, the elderly, patients with chronic renal failure and patients taking glucocorticoids, fever may not be present despite infection.

Management of patients with acute fever

First, the patient should be evaluated for signs of sepsis requiring prompt medical attention. Sepsis is characterized as systemic inflammatory response syndrome (SIRS), defined by the presence of *two or more* of the following criteria:

- temperature greater than 38°C or less than 35°C
- heart rate greater than 90 beats/minute
- respiratory rate greater than 20 breaths/minute or $PaCO_2$ less than 32 mmHg (4.3 kPa)
- leucocyte count greater than 12×10^9/L, less than 4×10^9/L or greater than 10% immature (band) forms

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in combination with either a culture-proven infection or an infection identified by visual inspection.[1]

In 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 count 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. Empirical antibiotic therapy should be instituted within 1 hour, according to local antibiotic prescribing policies (see also *MEDICINE* 2009; **37**(10): 562–565).

A history should include travel, occupation and leisure pursuits, sexual history, illicit parenteral drug use, animal contact and previous drug therapy, and, together with physical examination, should guide further management. In all patients with nuchal rigidity, a lumbar puncture (LP) should be performed (total and differential leucocyte count, protein level, cerebrospinal fluid:blood glucose ratio and Gram stain and culture) as soon as possible. An LP should be considered in patients with otherwise unexplained fever, suffering from a headache, photophobia, altered mental status or other neurological symptoms.

Fever in the returning traveller

Fever is a common feature of imported infections, about 40% of which will typically be 'tropical', about 35% 'cosmopolitan' and about 25% undefined or other causes. Diagnosis requires a complete travel history, including details of the countries visited, type of travel (urban vs rural), dates of travel, and activities were undertaken. This should encompass risk behaviours such as ingesting raw meat or fish, or unpasteurized milk products, swimming in fresh water, hobbies (such as caving), animal contact and sexual history, together with adherence to antimalarial chemoprophylaxis and pre-travel vaccination schedules.

The presence of fever should be confirmed, although traditional fever patterns are rarely useful in diagnosis. Examination should look for lymphadenopathy, rashes, eschars of tick or mite bites, jaundice, focal chest signs, hepatosplenomegaly or hepatic tenderness. Baseline investigations must include blood films, (see *MEDICINE* 2010; **38**(1): 30–5) usually supplemented by antigen tests for malaria if the traveller has been to a malaria endemic area. Although there is considerable overlap, the combination of splenomegaly, hyperbilirubinaemia and thrombocytopenia suggests malaria, the main differential diagnoses being dengue fever, chikungunya, and enteric fever. These are more likely than malaria in travellers from the Indian subcontinent or Asia. Leptospirosis and tick or scrub typhus are found worldwide, and eosinophilia suggests worms or flukes, particularly schistosomiasis from Africa (see *MEDICINE* 2010; **38**(1): 30–5). Fever from sub-Saharan Africa is very likely to be due to falciparum malaria, which can rapidly be lethal, usually presenting within 1–3 months of returning. Most, but not all, malaria from further east is due to 'benign' malarial species; vivax malaria, for example, commonly presents up to 12 months after return (see *MEDICINE* 2010; **38**(1): 41–6).

Pyrexia of unknown origin

In 1961, pyrexia of unknown origin (PUO) was originally defined by Petersdorf and Beeson as an illness of more than 3 weeks' duration, fever higher than 38.3°C (101°F) on several occasions and diagnosis uncertain after 1 week of study in hospital.[2] This definition has been modified, removing the requirement that the evaluation must take place in the hospital and refined to include four different sub-groups, each requiring different investigative strategies: classical, nosocomial, neutropenic and human immunodeficiency virus (HIV)-related. At the extremes of age PUO should also be considered separately. In the over 65s, the presentation, underlying conditions and subsequent treatment differ considerably from the younger age group. Pre-morbid condition must also be considered and, although many of the causes are treatable, not all older patients will be able to undergo rigorous invasive investigation. In some patients it may be inappropriate to investigate at all.[3] In children, the aetiology of PUO is similar but infection is more likely and accounts for over 50% of final diagnoses.[4]

The quantitative criterion (diagnosis uncertain after 1 week of study) has been changed to a qualitative criterion that requires a list of certain investigations to be performed to reduce selection bias.[5–7] 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 (Table 1). HIV testing should be undertaken in all patients irrespective of risk.

Causes of pyrexia of unknown origin

Table 2 presents an overview of the common causes of 'classic' PUO. Many studies have shown that PUO is more often caused by an atypical presentation of a common disease than by something exotic.[8,9] In general, infection accounts for about

Definition of pyrexia of unknown origin

- Fever higher than 38.3°C (101°F) on three occasions
- More than 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 the normal value), use of the equivalent of more than 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 count and differential, 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, HIV test

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 1

Common causes of classical pyrexia of unknown origin (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 infection, Coxsackievirus infection, Epstein—Barr virus infection, hepatitis A, B, C, or E, human immunodeficiency virus infection, parvovirus infection
Fungal	Endemic mycosis, aspergillosis, candidiasis, cryptococcosis, histoplasmosis
Parasitic	Malaria, leishmaniasis
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
Connective tissue disorders	
Systemic rheumatic diseases	Ankylosing spondylitis, Behçet's disease, cryoglobulinaemia, dermatomyositis, Felty's syndrome, gout/pseudogout, mixed connective tissue disease, polymyositis, Reiter's syndrome, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome
Vasculitis	Giant cell vasculitis/polymyalgia rheumatica Churg—Strauss syndrome, polyarteritis nodosa, Takayasu's arteritis, Wegener's granulomatosis
Granulomatous diseases	Sarcoidosis
Miscellaneous	Drug fever, factitious fever, inflammatory bowel disease, familial Mediterranean fever (FMF), haemophagocytic syndrome, Still's disease, adrenal insufficiency, amyloidosis, atrial myxoma, auto-immune haemolytic anaemia, auto-immune hepatitis, Castleman's disease, hyperthyroidism, Kawasaki's syndrome, phaeochromocytoma, pulmonary embolism/thrombosis

one-quarter of cases of PUO, followed by neoplasm and non-infectious inflammatory diseases (NIID).[8] The category NIID includes systemic rheumatic diseases, vasculitis syndromes, granulomatous disorders and auto-inflammatory syndromes. In recent series of PUO, no diagnosis could be reached in up to 50% of all cases.[7,10] In patients with recurrent fever, often defined as repeated episodes of fever with fever-free intervals of at least 2 weeks and apparent remission of the underlying disease, the chance of reaching a diagnosis is less than 50%. Recent advances in microbiological diagnostics and imaging modalities have reduced the proportion of cases where the cause is unknown.

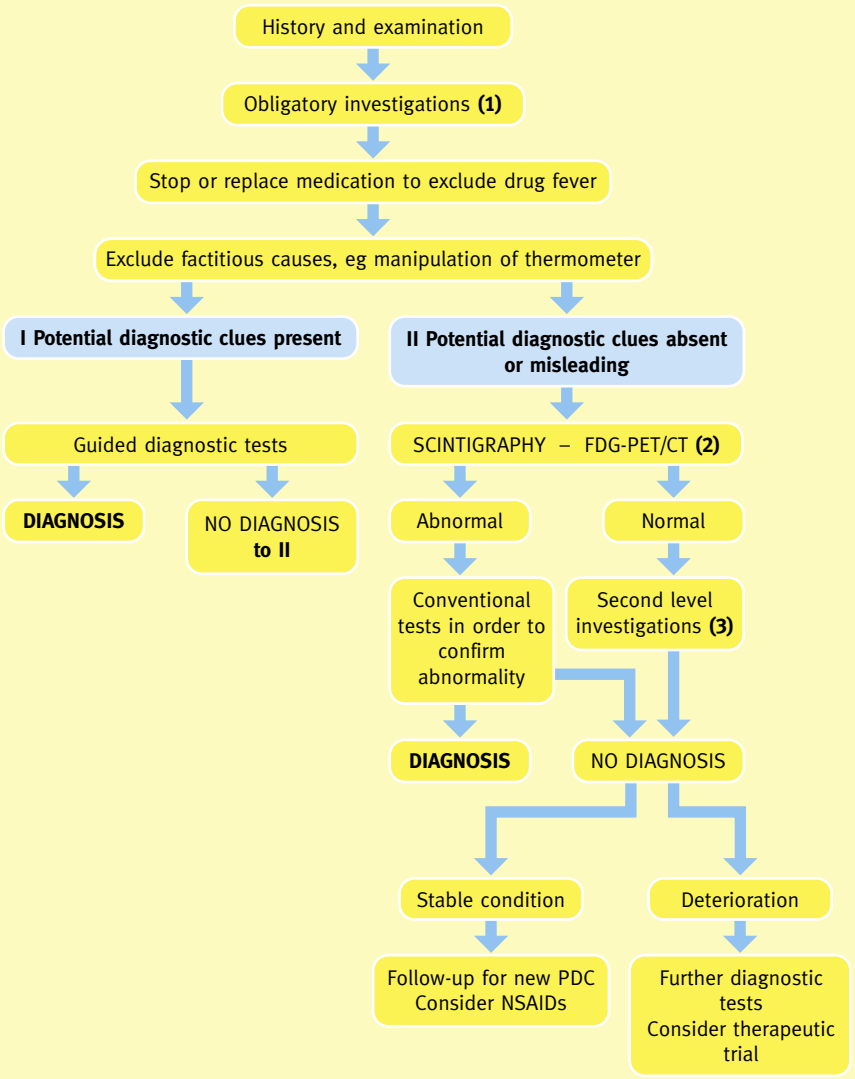
Diagnostic algorithm for pyrexia of unknown origin

Because of the diversity of causes of long-standing fever, it is difficult to construct algorithms that cover the complete spectrum of PUO. A proposed algorithm is shown in Figure 1. The most important step in the diagnostic work-up is complete and repeated history-taking, physical examination and the obligatory investigations in a search for potentially diagnostic clues (PDC). PDC are defined as all localizing signs, symptoms and abnormalities potentially pointing towards a diagnosis,[11] and are summarized in Table 3. Although often misleading, a limited list of probable diagnoses can be made only with the help of these PDC. Clinicians should perform a complete physical examination, with special attention to the lymph nodes, temporal arteries, sites of previous surgery, and the entire skin surface and mucous membranes, including rectal examination, search for dental sepsis and fundoscopy. Specific findings leading to a diagnosis in PUO are numerous and diverse, but can often be detected only by a very careful examination and may be missed the first time. In the absence of PDC, the physical examination should be repeated regularly.

Factitious fever should be excluded, particularly in patients without signs of inflammation on laboratory testing. All medications, including non-prescription drugs and nutritional supplements, should be discontinued (if possible) early in the evaluation to exclude drug fever. The length of time of previous use is irrelevant since medications taken without problems for years can cause fever at any time. If fever persists beyond 72 hours after discontinuation of the suspected drug it is unlikely that this drug is the cause. After identification of all PDC retrieved from the history, physical examination and obligatory tests, a limited list of most probable diagnoses should be made. Since most investigations are helpful only when performed in patients with PDC related to the suspected diagnoses further diagnostic procedures should be limited to specific investigations used to confirm or exclude those diseases. In patients without PDC or only misleading PDC, repeat fundoscopy and cryoglobulins may be useful in the early phase of the diagnostic work-up.[11]

In a later phase, nuclear imaging techniques are useful non-invasive tests in patients without PDC. While important when considering infective endocarditis, the value of echocardiography has been overemphasized in the investigation of true PUO and is rarely if ever useful in the absence of suggestive PDC. In possible endocarditis, transoesophageal echocardiography (sensitivity 95—100%, specificity 98% for endocardial vegetations) is preferable to transthoracic echocardiography (sensitivity 63%, specificity 98%).[13] Temporal artery biopsy in patients older than 55 years, and bone marrow biopsy, can be useful in patients without PDC.[7] A recent retrospective analysis of 130 patients with PUO who underwent bone marrow biopsy revealed a diagnostic yield in 23.7%, particularly in the

Diagnostic algorithm in patients with pyrexia of unknown origin



1. Obligatory tests for the definition of fever of unknown origin are shown in Table 1. These may be extended to include fundoscopy and serum for cryoglobulins. **2.** ^{67}Gallium citrate, ^{111}indium-labelled or ^{99}mtechnetium-labelled leukocytes or ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) can be used. Because of favourable characteristics of FDG-PET/CT, we believe that conventional scintigraphic techniques should be replaced by FDG-PET/CT in institutions where it is available. FDG-PET/CT may be performed after the first-stage investigations, but placing scintigraphic imaging after the second-stage investigations is also a common strategy. **3.** Second-stage investigations are temporal artery biopsy in patients older than 55 years, bone marrow biopsy, abdominal CT and chest CT. PDC, potential diagnostic clues; NSAID, non-steroidal anti-inflammatory drug.

Figure 1

presence of thrombocytopenia or anaemia.[14] However, second-stage investigations should be determined by local epidemiological data and the diagnostic facilities available. In patients with unexplained fever at this point, the last step in the diagnostic work-up comes at a high cost and discomfort with a marginal diagnostic yield.

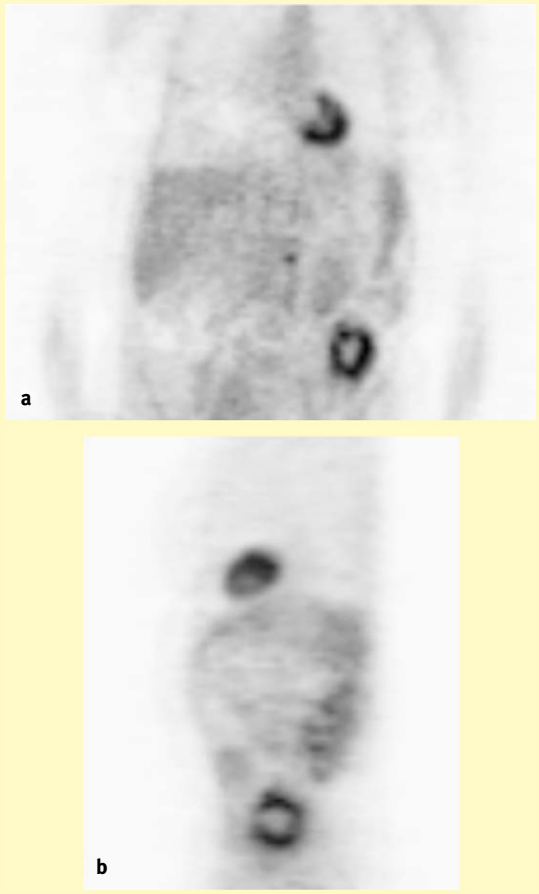
Repeating a thorough history-taking, physical examination and reviewing laboratory results and imaging studies, including those from other hospitals, is recommended. Delay often results from the failure to recognize helpful clues in available information. In patients with persisting PUO, waiting for new PDC to appear probably is better than ordering more screening investigations. Only in the rare patient who deteriorates without presenting new PDC should a further diagnostic work-up be performed.

In patients with familial fever or recurrent fever for more than 2 years, it is very unlikely that the fever is being caused by infection or malignancy. In these patients, the diagnostic work-

Potential diagnostic clues and associated diagnoses (adapted from Varghese et al[12])

Altered mentation — meningitis (tuberculous, carcinomatous), encephalitis (viral and non-infectious causes), malaria, African trypanosomiasis, brucellosis, sarcoidosis, syphilis, Whipple's disease, central nervous system vasculitis
Animal contact — brucellosis, toxoplasmosis, psittacosis, leptospirosis, Q fever, cat scratch disease
Arthritis/arthralgia — infective endocarditis, brucellosis, infective endocarditis, systemic lupus erythematosus, inflammatory bowel disease, Whipple's disease
Cough — tuberculosis, sarcoidosis, Q fever, enteric fever
Conjunctival suffusion — leptospirosis, relapsing fever
Epistaxis — Wegener's granulomatosis, relapsing fever
Epididymo-orchitis — tuberculosis, lymphoma, polyarteritis nodosa, brucellosis, infectious mononucleosis, leptospirosis
Hepatomegaly — lymphoma, disseminated tuberculosis, liver metastases, hepatitis (granulomatous, auto-immune, alcoholic), hepatoma, Q fever, relapsing fever, typhoid fever, malaria, visceral leishmaniasis, hydatid, brucellosis
Lymphadenopathy — lymphoma, tuberculosis, infectious mononucleosis, cytomegalovirus, toxoplasmosis, HIV, brucellosis, cat scratch disease, Kikuchi's disease.
Rash — drug reactions, vasculitis, Sweet's syndrome, Kawasaki's disease, malignancy, lymphoma, sarcoidosis, leprosy reactions
Sexual history — HIV, syphilis
Splenomegaly — lymphoma, leukaemia, visceral leishmaniasis, malaria infectious endocarditis, infectious mononucleosis, cytomegalovirus, tuberculosis, sarcoidosis, rheumatoid arthritis, adult Still's disease
Splenic abscess — infectious endocarditis, enteric fever, melioidosis, brucellosis
Travel history — wide differential, especially malaria (including late presentations), enteric fever, brucellosis, African trypanosomiasis, visceral leishmaniasis
Uveitis — tuberculosis, sarcoidosis, inflammatory bowel disease, adult Still's disease, systemic lupus erythematosus, Behçet's disease, Lyme disease, leprosy reactions

Table 3



FDG-PET in a 61-year-old patient with pyrexia of unknown origin. This 61-year-old woman had had episodes of fever lasting from 7 to 40 days from about 8 years old. Except for fatigue, anorexia and weight loss during a fever episode, she had no complaints. An extensive diagnostic work-up in two different hospitals had not resulted in an explanation for her fever. The fever subsided spontaneously, but appeared to resolve faster with antibiotic treatment. PET, performed during a fever episode, showed abnormal FDG-uptake in the sigmoid (**a** coronal slice, **b** sagittal slice). Abdominal CT (which had shown normal results during an earlier asymptomatic phase) was performed the next day and demonstrated diverticulitis. FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computed tomography.

Figure 2 FDG-PET in a 61-year-old patient with pyrexia of unknown origin. This 61-year-old woman had episodes of fever lasting from 7 to 40 days from age 8 years. Except for fatigue, anorexia and weight loss during a fever episode, she had no complaints. An extensive diagnostic work-up in two different hospitals had not resulted in a diagnosis. The fever subsided spontaneously, but appeared to resolve faster with antibiotic treatment. PET, performed during a fever episode, showed abnormal FDG-uptake in the sigmoid (**a** coronal slice, **b** sagittal slice). Abdominal CT (which had shown normal results during an earlier asymptomatic phase) was performed the next day and demonstrated diverticulitis. FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computerized tomography.

up should consist of thorough history-taking, physical examination and obligatory investigations. Only when PDC for infections, vasculitis syndromes or malignancy are present, or when the clinical condition is deteriorating, should further diagnostic tests be considered. Systemic investigations should preferably be performed during a symptomatic phase.

Scintigraphic imaging

Scintigraphic methods play an important role in the diagnostic process of patients with PUO. Their exact place in the order of diagnostic procedures remains unclear, but in the diagnostic algorithm, a possible order is shown (Figure 1). Conventional radiopharmaceuticals routinely used in patients suspected of infectious or inflammatory disease, such as ^{67}gallium citrate (^{67}Ga) and ^{111}indium-labelled or ^{99m}technetium-labelled

leucocytes (WBC), have disadvantages and limitations, such as handling of potentially infected blood products (WBC), high radiation burden (^{67}Ga) and the long time-span between injection and diagnosis (^{67}Ga).

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is increasingly being used in PUO and detects malignant processes as well as infectious and inflammatory disorders, but is not always able to differentiate between those disorders (Figure 2). Fluoro-2-deoxy-D-glucose is preferentially taken up by cells such as tumour and inflammatory cells, in which glucose metabolism is high. The diagnostic yield may be increased further by using FDG-PET simultaneously with conventional computed tomography (CT).[15,16] Compared to conventional nuclear medicine techniques, other advantages of FDG-PET are early imaging (1 h), higher resolution, and sensitivity in chronic low-grade infections, infections of the central skeleton and vasculitis.

A multicentre study of almost 300 patients with PUO showed that FDG-PET had an overall helpfulness of 36%, which is much better conventional imaging techniques.[8,10,17] FDG-PET, with or without CT, never contributed to a diagnosis in cases with repeatedly normal CRP or erythrocyte sedimentation rate.[6] It is most useful in the investigation of patients without localizing PDCs but evidence of active inflammation. In patients with recurrent fever, scintigraphic imaging should be performed only during a symptomatic phase

As a result of the favourable characteristics of FDG-PET/CT, conventional scintigraphic techniques may be replaced by FDG-PET/CT in institutions where it is available. When ordered early in the diagnostic work-up, FDG-PET/CT enables identification of the organ or tissue where the cause of the fever is likely to be found and appears to be cost-effective.[18] Abnormal results can then be used for guiding intelligent further testing.

Management

If the fever persists and the source remains elusive after completing the second-stage investigations, treatment with non-steroidal anti-inflammatory drugs may help symptomatically. Therapeutic trials with antibiotics, corticosteroids or anti-tuberculous agents should be avoided, except in the deteriorating patient.

Prognosis

Prognosis is determined primarily by the underlying disease and also by speed of diagnosis. However, most patients with undiagnosed PUO have benign self-limiting or recurrent fever. In two-thirds of cases, fever will resolve by 2 years with 3% mortality in this group at 5 years.[19] ◆

REFERENCES

1 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20:** 864–74.

2 Petersdorf RG, Beeson PB. Fever of unexplained origin: report on100 cases. *Medicine* 1961; **40:** 1–30.

3 Todd S, Beeching NJ. Fever of unknown origin. Chapter 11. In: Gosney M, Harper A, Conroy S, eds. The Oxford desk reference: geriatric medicine. Oxford University Press, 2012; 248–49.

4 Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. *World J Pediatr* 2011; **7:** 5–10.

5 Petersdorf RG. Fever of unknown origin. An old friend revisited. *Arch Intern Med* 1992; **152:** 21–2.

6 Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. *J Intern Med* 2003; **253:** 263–75.

7 Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. *Medicine (Baltimore)* 2007; **86:** 26–38.

8 Bleeker-Rovers CP, Vos FJ, Mudde AH, et al. A prospective multi-centre study of the value of FDG-PET as part of a structured diagnostic protocol in patients with fever of unknown origin. *Eur J Nucl Med Mol Imaging* 2007; **34:** 694–703.

9 Arnow PM, Flaherty JP. Fever of unknown origin. *Lancet* 1997; **350:** 575–80.

10 Buysschaert I, Vanderschueren S, Blockmans D, Mortelmans L, Knockaert D. Contribution of (18)fluoro-deoxyglucose positron emission tomography to the work-up of patients with fever of unknown origin. *Eur J Intern Med* 2004; **15:** 151–6.

11 de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. *Medicine (Baltimore)* 1997; **76:** 392–400.

12 Varghese GM, Trowbridge P, Doherty T. Investigating and managing pyrexia of unknown origin in adults. *Br Med J* 2010; **341:** c5470.

13 Erbel R, Rohmann S, Drexler M, et al. Improved diagnostic value of echocardiography in patients with infective endocarditis by trans-oesophageal approach. A prospective study. *Eur Heart J* 1988; **9:** 43–53.

14 Hot A, Jaisson I, Girard C, et al. Yield of bone marrow examination in diagnosing the source of fever of unknown origin. *Arch Intern Med* 2009; **169:** 2018–23.

15 Ferda J, Ferdova E, Zahlava J, Matejovic M, Kreuzberg B. Fever of unknown origin: a value of 18F-FDG-PET/CT with integrated full diagnostic isotropic CT imaging. *Eur J Radiol* 2010; **73:** 518–25.

16 Balink H, Collins J, Bruyn GA, Gemmel F. F-18 FDG PET/CT in the diagnosis of fever of unknown origin. *Clin Nucl Med* 2009; **34:** 862–8.

17 Federici L, Blondet C, Imperiale A, et al. Value of (18)F-FDG-PET/CT in patients with fever of unknown origin and unexplained prolonged inflammatory syndrome: a single centre analysis experience. *Int J Clin Pract* 2010; **64:** 55–60.

18 Becerra Nakayo EM, García Vicente AM, Soriano Castrejón AM, et al. Analysis of cost-effectiveness in the diagnosis of fever of unknown origin and the role of ^{18}F-FDG PET-CT: a proposal of diagnostic algorithm. *Rev Esp Med Nucl Imagen Mol* 2012; **31:** 178–86. (Epub ahead of print 5 Dec 2011).

19 Knockaert DC, Dujardin KS, Bobbaers HJ. Long-term follow-up of patients with undiagnosed fever of unknown origin. *Arch Intern Med* 1996; **156:** 618–20.

FURTHER READING

Armstrong W, Powel Kazanjian. Fever of unknown origin. In: Cohen J, Opal SM, Powderly WG, eds. Infectious diseases. London: Mosby/Elsevier, 2010; 871–880.

Practice points

- Patients with acute fever should be evaluated for signs of sepsis because they require prompt medical attention
- The key to PUO diagnosis is thorough and repeated history-taking and clinical examination, combined with baseline investigations to elicit potential diagnostic clues (PDC)
- 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 may be replaced by FDG-PET/CT in institutions where it is available
- Since many patients with undiagnosed PUO have benign self-limiting or recurrent fever, therapeutic trials with antibiotics, corticosteroids or anti-tuberculous agents should be avoided, except in patients whose condition is deteriorating

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