Investigating and managing pyrexia of unknown origin in adults

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Few clinical problems generate such a wide differential diagnosis as pyrexia (fever) of unknown origin. The initial definition proposed by Petersdorf and Beeson in 1961,[1] later revised, is "a fever of 38.3°C (101°F) or more lasting for at least three weeks for which no cause can be identified after three days of investigation in hospital or after three or more outpatient visits."[2-4] Essentially the term refers to a prolonged febrile illness without an obvious cause despite reasonable evaluation and diagnostic testing. A fever that is not self limiting for which no cause can be found can become a source of frustration for both patient and doctor. There is little consensus on how such patients should be investigated, although recent prospective studies have evaluated diagnostic protocols to suggest approaches to investigation.[3 5 6] We discuss evidence from epidemiological and diagnostic studies and suggest an approach to investigating and managing pyrexia of unknown origin.

Immunocompromised individuals, those with HIV infection, and patients admitted to hospital for other reasons with persistent or unexplained fever represent distinct subgroups in which the likely causes, diagnosis, and treatment of pyrexia usually differ from those in patients who are not immunocompromised. We do not discuss these subgroups in this review other than to provide definitions of pyrexia of unknown origin in different groups of patients (see box 1).

Box 1 | Classifications of pyrexia of unknown origin

Classic pyrexia of unknown origin—Pyrexia for ≥3 weeks with no identified cause after evaluation in hospital for 3 days or ≥3 outpatient visits.

Nosocomial pyrexia of unknown origin—Pyrexia in patients hospitalised for >48 hours with no infection present or incubating at admission, and in whom the diagnosis remains uncertain after ≥3 days of appropriate evaluation, which includes microbiological cultures that have been incubating for ≥2 days.

Immunodeficient (neutropenic) pyrexia of unknown origin—Pyrexia in a patient with <500 neutrophils/µl in whom the diagnosis remains uncertain after ≥3 days of appropriate evaluation, which includes microbiological cultures that have been incubating for ≥2 days.

HIV-associated pyrexia of unknown origin—Pyrexia in a patient with confirmed HIV infection lasting for >4 weeks as an outpatient or >3 days as an inpatient, in whom the diagnosis remains uncertain after ≥3 days of appropriate evaluation, which includes microbiological cultures that have been incubating for ≥2 days.

As classified by Durack and Street.[4]

SOURCES AND OTHER SELECTION CRITERIA

We searched for papers that were published between 1966 and August 2010 using appropriate MESH terms (pyrexia of unknown origin, fever of unknown origin) in the National Library of Medicine's computerised search service (PubMed and other related databases). We also consulted Cochrane database systematic reviews. We reviewed all relevant articles as well as the cited references to identify further articles.

SUMMARY POINTS

Classic adult pyrexia of unknown origin is fever of 38.3°C or greater for at least 3 weeks with no identified cause after three days of hospital evaluation or three outpatient visits

Common causes are infections, neoplasms, and connective tissue disorders

A thorough history and physical examination, along with basic investigations will usually provide clues to a possible diagnosis that can guide the choice of further investigations

If the initial evaluation provides no diagnostic clues, further investigations including imaging studies and serological tests may be indicated

A watch and wait approach is acceptable in a clinically stable patient for whom no diagnosis can be made after extensive investigation, and the prognosis is likely to be good

Empirical antibiotics are warranted only for individuals who are clinically unstable or neutropenic. In stable patients empirical treatment is discouraged, although NSAIDs may be used after investigations are complete. Empirical corticosteroid therapy is discouraged

How common is pyrexia of unknown origin?

The true incidence and prevalence of pyrexia of unknown origin are uncertain. A study of 153 patients reported the prevalence in hospitalised patients in the 1980s to be around 3%.[7] However, in the past two decades technological advances in diagnosis, particularly sophisticated imaging and improved culture techniques, have reduced the proportion of cases where the cause is unknown.[6]

What causes pyrexia of unknown origin?

Pyrexia of unknown origin has a wide differential diagnosis. The most frequently encountered underlying causes of the pyrexia are listed in box 2. Broadly speaking, the three most common causes are infection, neoplasia, and connective tissue disease. Many prospective and retrospective studies have shown that pyrexia of unknown origin is more often caused by an atypical presentation of a common disease than by something exotic.[5 6] Although causes of pyrexia of unknown origin vary substantially across geographical areas, a recent well conducted prospective cohort study and another retrospective evaluation from Europe reported the following proportions[8 9]—infection 15-30%, neoplasia 10-30%, connective tissue disease 33-40%, miscellaneous (such as

drug fever, hyperthyroidism, and factitious fever) 5-14%, undiagnosed 20-30%.

Data from several large prospective studies suggest that infective causes are becoming less common, probably because advanced imaging techniques and improved culture methods have become more widely available.[10-12] For similar reasons, the proportion of cases of pyrexia of unknown origin attributed to neoplasia has steadily decreased over recent years.[5-13] These trends do not hold true in less developed societies where infection, often with mycobacteria, remains common and advanced diagnostic techniques are often unavailable.[14-16] Worth noting is that miscellaneous disorders are fairly common (see above).

Box 2 | Common causes of fever of unknown origin

Infection
Abdominal abscess
Extrapulmonary/disseminated tuberculosis
Infective endocarditis
Osteoarticular infections
Typhoid/enteric fevers
Endemic mycosis
Epstein-Barr virus infection
Cytomegalovirus infection
Brucellosis
Leishmaniasis
Prostatitis
Malaria
Rickettsial infections
Dental abscess
Chronic sinusitis

Neoplasm
Lymphoma
Hepatoma
Hepatic metastasis
Renal cell carcinoma
Leukaemia
Colon cancer
Pancreatic cancer

Connective tissues disorder
Systemic lupus erythematosis
Adult onset Still's disease
Autoimmune hepatitis
Systemic vasculitis
Mixed connective tissue disease
Polymyalgia rhematica
Inflammatory bowel disease
Sarcoidosis
Kikuchi's disease

Miscellaneous
Drug fever
Factitious fever
Mediterranean familial fever
Deep vein thrombosis/pulmonary embolism
Hyperthyroidism

How is pyrexia of unknown origin investigated?

Initial approach

History

Taking a thorough history and physical examination may often lead to a diagnosis. Repeating the history several times may elicit previously overlooked clues. Consider all symptoms as relevant since most patients with pyrexia of unknown origin present with a common disease that is atypically manifested.[5 6] Eliciting a history of comorbid conditions and previously treated diseases such as endocarditis, tuberculosis, rheumatic fever, and cancer may provide important diagnostic clues. A surgical history that provides information about the type of surgery performed, postoperative complications and any indwelling foreign material could also be relevant. Travel history is important because it may provide information about possible exposure to endemic diseases such as malaria, histoplasmosis, or other fungal infections.

Potentially important clues may be found in aspects of the history that are not routinely discussed with patients, such as the sexual history; asking about specifics of sexual practices such as anal penetration leading to rectal abscesses may point to a possible source of infection. Ask about social habits, such as drug use, exposure to animals or pets, specifics of the patient's employment and hobbies. Enquire about unusual dietary habits, such as consumption of unpasteurised dairy products or rare meats. Check for any recent changes in medication that could have contributed to unexplained fever. A full obstetric and gynaecological history in women may provide clues to the underlying condition; for example a history of multiple miscarriages may suggest a connective tissue disease or pelvic pain may suggest tubo-ovarian pathology.

Documenting fever

A persistent fever needs to be accurately documented because the pattern of the fever and its relation with the pulse rate (particularly a temperature-pulse disparity) may point to an underlying cause. Accurate charting of the fever may require admission to hospital. Temperature-pulse disparity may have diagnostic relevance in infections with intracellular organisms such as typhoid, brucellosis, and legionellosis.

Careful physical examination

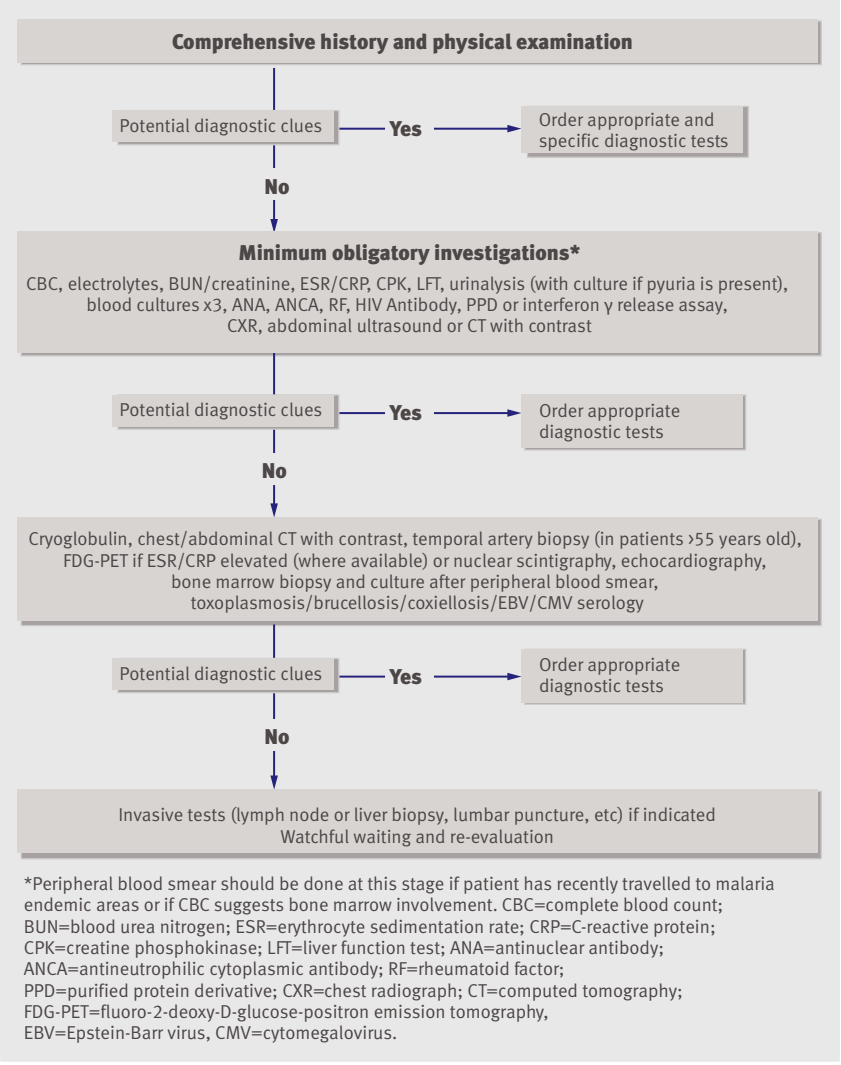
Fever could arise from pathology in any system, so a thorough physical examination is important. It should include a full neurological examination, musculoskeletal, ear-nose-throat, dermatological, lymphatic, and urogenital examinations, and fundoscopy. Box 3 lists some common symptoms and signs and the causes of pyrexia that may be associated with them. Some well known causes of pyrexia of unknown origin are associated with particular signs; for example, temporal artery tenderness in temporal arteritis, lymphadenopathy in lymphoma and disseminated tuberculosis, and a heart murmur in bacterial endocarditis. Some clinical findings, although rare, are virtually diagnostic, such as Roth's spots in infective endocarditis.

Box 3 | Common signs and symptoms and associated causes of pyrexia

- Altered mentation—tuberculous meningitis, cryptococcal meningitis, carcinomatous meningitis, brucellosis, typhoid fever, sarcoid meningitis
- Arthritis or arthralgia—systemic lupus erythematosus, infective endocarditis, Lyme disease, lymphogranuloma venereum, Whipple's disease, brucellosis, inflammatory bowel disease
- Animal contact—brucellosis, toxoplasmosis, cat scratch disease, psittacosis, leptospirosis, Q fever, rat bite fever
- Cough—tuberculosis, Q fever, typhoid fever, sarcoidosis, Legionnaires' disease
- Conjunctival suffusion—leptospirosis, relapsing fever, Rocky Mountain spotted fever
- Epistaxis—Wegener's granulomatosis, relapsing fever, psittacosis
- Epididymo-orchitis—tuberculosis, lymphoma, polyarteritis nodosa, brucellosis, leptospirosis, infectious mononucleosis
- Hepatomegaly—lymphoma, disseminated tuberculosis, metastatic carcinoma of liver, alcoholic liver disease, hepatoma, relapsing fever, granulomatous hepatitis, Q fever, typhoid fever, malaria, visceral leishmaniasis
- Lymphadenopathy—lymphoma, cat scratch disease, tuberculosis, lymphomogranuloma venereum, infectious mononucleosis, cytomegalovirus infection, toxoplasmosis, HIV infection, brucellosis, Whipple's disease, Kikuchi's disease
- Renal angle tenderness—perinephric abscess, chronic pyelonephritis
- Splenomegaly—leukaemia, lymphoma, tuberculosis, brucellosis, subacute bacterial endocarditis, cytomegalovirus infection, Epstein-Barr virus mononucleosis, rheumatoid arthritis, sarcoidosis, psittacosis, relapsing fever, alcoholic liver disease, typhoid fever, Kikuchi's disease
- Splenic abscess—subacute bacterial endocarditis, brucellosis, enteric fever, melioidosis
- Subconjunctival hemorrhage—infective endocarditis, trichinosis, leptospirosis
- Uveitis—tuberculosis, sarcoidosis, adult Still's disease, systemic lupus erythematosus, Behcet's disease

Basic investigations

The approach to investigating any patient with pyrexia of unknown origin should ideally be focused according to the patient's presentation and clinical signs. Basic laboratory and imaging studies may help to guide further evaluation. No list of tests has been widely accepted as being the minimal obligatory investigations, but basic investigations that have been suggested and used by researchers and clinicians in several studies [3-11] are listed in the first part of the diagnostic algorithm (fig 1). Additional testing for atypical presentations of diseases that are specific to certain regions, such as Lyme disease, malaria, or histoplasmosis, may also be indicated.



Algorithm for evaluation of fever of unknown origin

Further investigations

Clues gleaned from the history, physical examination, and first round of diagnostic evaluations should be the basis for subsequent investigations that are tailored to the individual patient as shown in the diagnostic algorithm (fig 1). However, in the absence of potential clues, there are some data directing what further studies are of utility. Recent prospective studies have highlighted the usefulness of early use of FDG-PET ([18F] fluoro-2-deoxy-D-glucose positron emission tomography), which may be useful in helping to pinpoint a source of fever.[10 11 17] Fluoro-2-deoxy-D-glucose is preferentially taken up by cells such as tumour and inflammatory cells, in which glucose metabolism is high. In a systematic review of eight prospective and retrospective studies including 302 patients, FDG-PET localised pathology directing further tests that led to diagnosis in over a third of patients.[18] The diagnostic yield may be increased further by simultaneously using FDG-PET with conventional computed tomography (CT). Several small retrospective studies have shown sensitivities from 56% to100%, specificities from 75% to 81%, and negative predictive values of 100%, when a combination of CT and FDG-PET scanning is used.[19-21] Notably, FDG-PET was of no diagnostic benefit unless patients had an elevated erythrocyte sedimentation rate or raised concentrations of C-reactive protein.[18]

Nuclear scintigraphy, for example with ^{67}Ga-citrate and ^{111}In labelled leukocytes, is a much cheaper and more widely available imaging technique that may perform a similar role in localising pathology, though it is more time consuming and less sensitive and specific than FDG-PET. In a retrospective study evaluating the contribution of ^{67}Ga scintigraphy in 145 cases of pyrexia of unknown origin in Belgium between 1980 and 1989, only 29% of the scans were considered helpful in diagnosis and 49% of the abnormal scans were considered noncontributory to the diagnosis.[22] The limited specificity and the generally unfavourable characteristics of ^{67}Ga scintigraphy makes it less attractive than FDG-PET. A recent retrospective study including 31 patients with pyrexia of unknown origin, ^{111}In leukocyte scintigraphy was reported to be helpful in 19% of all cases.[23] However, the probability of reaching a diagnosis was observed in 71% with a sensitivity of 75% and specificity 83%. Leukocyte scintigraphy may be helpful in diagnosing inflammatory and infectious conditions and rarely of use in neoplasm.

Several studies, including two large multicentre prospective analyses, have looked at the usefulness of other investigations in the absence of diagnostic clues. The evidence from these studies supported the use of chest CT and abdominal CT or ultrasound (if not already performed), looking specifically for: abscesses, lymph nodes, or splenomegaly; cryoglobulins (mixed cyroglobulinaemia was surprisingly common even in the absence of known risk factors); and temporal artery biopsy, particularly in patients older than 55.[6 10] Although many previous studies supported temporal artery biopsy for patients older than 55 in the absence of clues indicating potential temporal arteritis, the authors thought this invasive procedure should be done later in the process of evaluation as temporal arteritis was a less prominent cause of pyrexia of unknown origin than previous studies had indicated.[10]

Evidence from one small but well done and recent retrospective analysis showed that bone marrow aspirate with trephine biopsy was diagnostic in nearly a fifth of patients and "helpful" for diagnosis in nearly a quarter. This was particularly, though not exclusively, true in the presence of thrombocytopenia or anaemia (haemoglobin <110 g/l). Bone marrow culture is thought to have a lower yield in immunocompetent individuals than in those who are immunocompromised, although this is probably less true in non-industrialised societies.[24] Echocardiography is a non-invasive test that may be useful even in people with negative blood culture and without an audible heart murmur. Transoesophageal echocardiography (which has a diagnostic sensitivity of 95-100%, and a specificity of 98% for endocardial vegetations) is preferable to transthoracic echocardiography (sensitivity 63%, specificity 98%).[25] Epstein-Barr virus, cytomegalovirus, toxoplasmosis, brucellosis, and coxiellosis are infections that can all present in a very non-specific way and serological tests for these infections may be useful. More invasive tests, such as lymph node or liver biopsy, and lumbar puncture, may be considered when the cause of fever remains unidentified after two step evaluation as described above and when clinical suspicion shows that these tests are indicated—see the later part of the diagnostic algorithm (fig 1).

ADDITIONAL EDUCATIONAL RESOURCES

- Cunha B. *Fever of unknown origin*. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious diseases*, 3rd ed. 2004—well written article appropriate for helping to generate a sound differential diagnosis based on organ involvement, symptoms, or epidemiological risk factors, with a wealth of resources available within the rest of the text for specifics of infectious diseases.
- Mandell GL, Bennett JE, Dolin R. *Principles and practice of infectious disease*, 7th ed. 2009, pp 779-89—comprehensive overview of pyrexia of unknown origin. The different types of pyrexia of unknown origin with causes and approach are separately discussed.
- *Infectious Disease Clinics of North America* 2007, 21:857-1232—an entire issue of *Infectious Disease Clinics of North America* devoted to pyrexia of unknown origin, with an emphasis on the diagnostic approach.

QUESTIONS FOR FUTURE RESEARCH

- Does early use of FDG-PET combined with CT hasten diagnosis and lower costs?
- What evaluations are cost-effective?
- What is a cost-effective obligatory evaluation in a resource limited setting?
- What effect does empiric treatment have on outcomes?
- Could international standardisation of definitions and evaluation lead to the creation of large database systems through which the epidemiology and management of pyrexia of unknown origin could be properly evaluated?
- What is the role of new tests such as serum procalcitonin in the evaluation of pyrexia of unknown origin?

What is a reasonable approach to management of pyrexia of unknown origin?

Once a diagnosis has been established specific treatment can be started. For patients in whom a cause for the fever is not found and who are not clinically unwell, watching and waiting is reasonable. During this time of observation re-assess the history and physical examination, stepping back to re-evaluate the data, and consider new avenues to pursue. One large prospective study found an attributable mortality of only 3.2% at five years in people with pyrexia of unknown origin where a specific diagnosis could not be reached.[26] The same study showed that most instances of pyrexia of unknown origin in which no diagnosis could be made resolved spontaneously, all of which suggests a good prognosis for people who remain without a diagnosis.[26]

In most cases where the individual is clinically stable experts consider empirical treatment to be unnecessary. Patients who are clinically unstable or neutropenic require prompt and appropriate antibiotic treatment. Empiric tuberculosis drugs may be considered where tuberculosis is prevalent and suspected but cannot be confirmed. Rifampicin may suppress fever even when not from an infectious cause. Empirical use of steroids is generally discouraged because it may mask symptoms and lead to delayed diagnosis of, for example, an underlying haematological malignancy. Several experts have recommended treatment with non-steroidal anti-inflammatory drugs for patients who have already had exhaustive investigations without finding an underlying cause. This treatment may be beneficial to patients in some situations, such as an underlying inflammatory condition. However, the theory that a patient's response to such drugs allows the doctor to differentiate neoplastic from other causes of pyrexia of unknown origin has been refuted.[27]

When a diagnosis remains elusive, a second opinion from a colleague in another medical specialty such as rheumatology, haematology, oncology, or infectious disease may be helpful.

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- Investigation and management of uveitis (*BMJ* 2010;341:c4976)
- Chronic pelvic pain in women (*BMJ* 2010;341:c4834)
- Head and neck cancer—Part 2 (*BMJ* 2010;341:c4690)
- Head and neck cancer—Part 1 (*BMJ* 2010;341:c4684)
- Diagnosis and management of Barrett's oesophagus (*BMJ* 2010;341:c4551)

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