Management of pyrexia of unknown origin

Introduction

Pyrexia of unknown origin is the term used to describe persisting fever without an obvious focus. A definition derived by Petersdorf and Beeson (1961) from analysis of 100 cases is as follows:

- Fever higher than 38.3°C on several occasions
- Duration of fever for at least 3 weeks
- Uncertain diagnosis after 1 week of study in the hospital.

True pyrexia of unknown origin is rare. Bleeker-Rovers et al (2007) studied admissions to a 950-bed academic referral hospital and five community hospitals comprising 2800 hospital beds in the Netherlands between December 2003 and July 2005; immunocompromised patients, such as those with acquired immunodeficiency syndrome (AIDS), hypogammaglobulinaemia, granulocytopenia and glucocorticoid therapy, were excluded. They identified only 73 patients with pyrexia of unknown origin and noted the following distribution of causes:

- Non-infectious inflammatory diseases (e.g. rheumatic diseases, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica) = 22%
- Infection = 16%
- Malignancy = 7%
- Miscellaneous = 4%
- No diagnosis = 51%.

Infections are more likely in younger patients, while multisystem diseases (inflammatory disease and sarcoidosis) account for a third of cases in patients over the age of 65 years.

Pyrexia which develops after admission to hospital and which remains undiagnosed is termed 'nosocomial pyrexia of unknown origin'. These patients are usually being treated for one or more major pre-existing conditions, and have multiple possible reasons for developing fever. After common bacterial infections such as pneumonia, urinary tract infection and bacteraemia have been excluded, many other conditions remain in the differential diagnosis: local or disseminated candidiasis, *Clostridium difficile* diarrhoea or colitis, cytomegalovirus infection, hepatitis, sinusitis (especially if the patient is intubated), intravascular catheter-related local or bloodstream infections, and infective endocarditis.

This article outlines an approach to managing pyrexia of unknown origin in an acute medical unit setting.

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History

Thorough history is crucial, addressing the various differential diagnoses and full systems review. Bleeker-Rovers et al (2007) found in their series of 73 patients that an average of 10.5 potential diagnostic clues per patient were gained through careful history and physical examination and three per patient through laboratory testing. The following questions should be covered:

- Localizing symptoms of infections:
  - cough, sputum production, shortness of breath
  - sore throat, sinusitis
  - headache, photophobia, neck stiffness, behavioural changes, seizures
  - diarrhoea, abdominal pain
  - dysuria, urinary frequency
  - skin ulcers, cuts, bites
  - rash, mylagia, arthralgia, jaw claudication, visual disturbance
  - night sweats, weight loss.
- Travel history (country visited and knowledge of prevalent infections including malaria, duration of foreign stay, date of return)
- Animal exposure (pets, occupational, living on a farm)
- History of insect or tick bites
- Intravenous illicit drug use, sexual history
- Immunosuppression (immunosuppressive drugs, steroid use, history of haematological disease or human immunodeficiency virus (HIV))
- Drug and toxin history, including antimicrobials and over-the-counter medications.

Examination

Full systems examination is required and should cover the following:

- Cardiovascular: murmurs (especially mitral or aortic regurgitation from endocarditis)
- Respiratory: signs of consolidation or effusion, associated brachial plexus involvement or Horner's syndrome suggesting apical lung carcinoma
- Abdominal: hepatomegaly, splenomegaly, masses, signs of chronic liver disease, ascites
- Meningism, focal neurology
- Skins ulcers, sacral sores
- Lymph nodes, joints, teeth
- Urogenital examination.

In practice the shape of the temperature curve is seldom of major value in the diagnosis of pyrexia of unknown origin. There is a common misconception that drug-induced fevers are usually low-grade ones, with relatively little variation from peak to trough and a relatively low pulse rate, but in fact the clinical characteristics of drug-induced fevers are highly variable. The degree of pyrexia, nature of the temperature curve, degree of systemic toxicity and response to antipyretics are not useful guides to the diagnosis of pyrexia of unknown origin (Hirschmann, 1997), but the course of the fever curve may be helpful in determining whether the disease is escalating or waning. However, it is important to remember that pyrexia may be attenuated in elderly, diabetic and immunosuppressed patients. Also, use of antipyretic, steroid and non-steroidal anti-inflammatory drugs can modify the clinical picture. In patients with pyrexia of unknown origin, it is important to explore symptoms and examine the patient daily.

Investigations

The following baseline tests should be performed on admission:

- Full blood count (including white cell count differential), urea and electrolytes, liver function
- Erythrocyte sedimentation rate and C-reactive protein – disproportionately raised erythrocyte sedimentation rate compared to C-reactive protein suggests an autoimmune aetiology

- Clotting screen: especially if haemodynamically compromised to screen for disseminated intravascular coagulation
- Blood cultures (peripherally and from any indwelling intravascular catheter, such as Hickman catheter): ideally before empirical antibiotic use (and if possible during the fever spikes) from different sites and different times of the day; prolonged culture may be needed for *Brucella*. At least three cultures should be performed, particularly if endocarditis is suspected.
- Urine: dipstick, specimen for microscopy and sensitivity
- Stool for microscopy and sensitivity, parasite, cysts or ova
- Sputum for microscopy and sensitivity; three early morning sputum samples for acid-fast bacilli if tuberculosis suspected
- Chest X-ray
- Electrocardiogram (look for PR prolongation in suspected aortic valve infection, ischaemic changes in myocarditis, saddled ST elevation in pericarditis)
- Echocardiogram (especially if a murmur is present).

Further investigations to consider depending on the clinical indications are:

- A peripheral blood film for abnormalities such as thrombocytosis, leukaemoid reactions, the presence of nucleated red blood cells, and other clues that the marrow is reacting to a pathological stimulus
- Serum lactate dehydrogenase level – very high levels (>500 iu/litre) are associated with lymphoma
- Thick and thin blood films for malaria, especially if the patient has a history of travel to the tropics. If there is a high index of suspicion, the films should be repeated every 8–12 hours
- Tuberculin skin test for *Mycobacterium tuberculosis* – although more reliable, this can be a cumbersome test to perform and an alternative is Elispot assay to detect antigen-recognizing T cells
- HIV antibody assay and HIV viral load in patients with risk factors (such as intravenous drug use and sexual exposure). If positive further tests searching for mycobacterium, *Pneumocystis carinii*, cytomegalovirus, cryptococcus and toxoplasma as the cause of the pyrexia should be considered
- Monospot or Paul-Bunnell tests to detect heterophile antibody in primary Epstein–Barr virus infection (glandular fever)
- Antistreptolysin O titre (raised in streptococcal infection)
- If history of tick bites and rash, consider serology for *Rickettsiae* and *Borrelia burgdorferi*. Skin biopsy should also be considered for immunohistochemistry, especially for the former
- Rheumatoid factor, antinuclear antibodies, creatine phosphokinase and temporal artery biopsy (if suspect connective tissue disorder)
- Serum protein electrophoresis (lymphoma, myeloma)
- Ferritin – can be elevated in any inflammatory process, but levels over five times the upper limit of normal raises the possibility of adult Still's disease
- Tumour markers (PSA, CA19-9, CEA, CA 125, AFP)
- Computed tomography scan of the head and lumbar puncture if neurological signs or confusion is present
- Computed tomography scan of chest, abdomen and pelvis (to localize abscesses or fluid collections)
- Adjunctive imaging with 67-gallium- or 111-indium-labelled leucocytes can be helpful if computed tomography fails to localize the source, but this can be costly and is of limited sensitivity. Positron emission tomography using isotopic fluorodeoxyglucose (FDG-PET scan) is a better choice and is usually available at specialist centres upon formal request.

Treatment approach

Treatment of the fever itself is indicated if it distresses the patient, exacerbates heart failure, or is severe enough to cause catabolism and wasting. Aspirin, paracetamol, or a non-steroidal anti-inflammatory drug in standard doses will usually suffice; a regular dosage schedule rather than occasional or 'as required' dosing is recommended.

If the patient is not sick, the temperature curve can be observed in the absence of treatment, often yielding useful new information while investigations continue. Ideally, a diagnosis should be made allowing specific therapy. If an aetiological diagnosis cannot be made at first, it is usually best to withhold treatment while observing the patient's progress at frequent intervals. Therapeutic trials of antimicrobials or corticosteroids rarely establish a diagnosis. Furthermore, the appropriate duration of a therapeutic trial is also unclear since a number of infections such as endocarditis or pelvic inflammatory disease can take as much as 1 week for fever to abate, even with appropriate therapy.

If an undiagnosed patient is too ill to permit prolonged observation, empirical treatment may be considered, but investigations should be continued in parallel. A common choice for empirical therapy is a broad-spectrum antibiotic, such as co-amoxiclav or fluoroquinolone, or a parenteral regimen including gentamicin. Input from the microbiology or infectious disease department is advisable to guide antibiotic choices and duration.

The other common choice for an empirical therapeutic trial is high dose corticosteroid. The possibility that the fever may be eliminated by empirical corticosteroid therapy while the primary disease is unaffected (or even exacerbated) should be kept in mind. In patients who are very ill, a combination of parenteral corticosteroid plus antibiotics may be required and medical care should be provided in a high dependency or intensive unit setting. Less commonly, empirical therapy for possible tuberculosis may be tried. It is important to remember that antimicrobial agents can suppress, but not cure, an infectious process such as an occult abscess since adjunctive drainage would usually be required. Broad-spectrum regimens, in addition, can have effects on infections other than the ones to which therapy is directed.

Prognosis

Although most of the causes of pyrexia of unknown origin can be treated, the 1-year mortality is still 20–30% (Longmore et al, 2001). The prognosis varies depending upon the underlying disease and the age of the patient. The diagnostic evaluation may fail to identify an aetiology in 30% of patients (Knockaert et al, 1996). If pyrexia of unknown origin persists undiagnosed for more than 6–12 months, the likelihood of a specific diagnosis ever being made decreases and the prognosis improves to <5% mortality.

The prognosis for nosocomial pyrexia of unknown origin depends largely on the underlying diagnoses. The overall prognosis for HIV-positive patients has markedly improved since the introduction of protease inhibitors and highly active retroviral treatment (expected survival of 10–15 years). Most of the causes of HIV-associated pyrexia of unknown origin can be treated, but the HIV disease is usually advanced by the time the patient has pyrexia of unknown origin. Atypical *Mycobacteria* spp. (which are the commonest cause of HIV-associated pyrexia of unknown origin) can be suppressed but rarely eliminated, and are likely to develop resistance to during therapy.

Conclusions

True pyrexia of unknown origin is rare. The key to managing a patient with pyrexia of unknown origin is taking a comprehensive history and performing a detailed physical examination at the time of admission, and to reassessing the patient daily. Clues gained this way will then guide further investigations. Infections are more likely in younger patients, while multisystem diseases (inflammatory disease and sarcoidosis) account for a third of cases in patients over the age of 65 years. In 30–50% of patients the aetiology may remain unknown. Ideally therapeutic trials with antibiotics or steroids should be avoided and definitive diagnosis should be sought to guide treatment unless the patient is very ill or neutropaenic. BJHM

KEY POINTS

- Pyrexia of unknown origin is defined as fever higher than 38.3ºC on several occasions lasting for at least 3 weeks without an established aetiology despite intensive evaluation and diagnostic testing.
- Three general categories of illness account for the majority of 'classic' pyrexia of unknown origin cases: infections, malignancies, and collagen vascular diseases.
- The incidence of specific aetiological agents of pyrexia of unknown origin varies by age of the population, potential exposure to infectious agents, host susceptibility to infection, and over time.
- The most important aspects of the evaluation of a patient with pyrexia of unknown origin are to take a careful history, perform a detailed physical examination, and to reassess the patient frequently.
- Initial investigations should include blood cultures, erythrocyte sedimentation rate, C-reactive protein, urine, stool and sputum samples for cultures, chest X-ray, electrocardiogram and echocardiogram.
- Ideally therapeutic trial with antibiotics or steroids should be avoided; a diagnosis should be sought to guide treatment.
- The diagnostic evaluation may fail to identify an aetiology in 30–50% of patients. Most adults who remain undiagnosed have a good prognosis.

Conflict of interest: none.

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Further reading

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