Pyrexia of unknown origin in clinical practice

This article revisits concepts of pyrexia of unknown origin to reflect current clinical practice. It describes the evolution of the term, in line with the changing spectrum and pace of investigations, and introduces key questions that may be used to evaluate a pyrexia of unknown origin.

Fever as a presenting symptom has always intrigued physicians (Chadwick and Mann, 1950). Several centuries of work by many physicians and scientists has been devoted to recording a patient's temperature, from Galileo's crude device in 1593 to Albert's portable thermometer in 1867. Since then, the characterization of an elevated body temperature became a pre-occupation that continues to the present day (Horder, 1925).

Clinicians increasingly acknowledged that some fevers persist, and pose a particular challenge to diagnose and treat (Alt and Barker, 1930; Kintner and Rowntree, 1934; Hamman and Wainwright, 1936; Wolf and Jacobs, 1947). In the 1960s Petersdorf and Beeson formalized a definition for an undetermined fever, 'fever of unexplained origin' (*Table 1*). They implemented the concept in a prospective study of 100 cases over 5 years. Their published article is a compelling read, with many aspects that hold true today such as the importance of a tissue diagnosis. The term 'pyrexia of unknown origin' was originally used to describe trench fever, but is now used interchangeably with fever of unexplained origin (Davies and Weldon, 1917; Wong and Lam, 1995).

Table 1. Definitions of pyrexia or fever of unknown origin

Reference	Definition
Horder (1925)	Sub-acute or chronic pyrexia in cases without physical signs
Petersdorf and Beeson (1961)	Fever of >38°C on several occasions for 3 weeks including 1-week inpatient investigation
Durack and Street (1991)	Fever of >38°C on several occasions for 3 weeks including 3 days inpatient investigation or outpatient visits. Categories defined as classic, nosocomial, neutropaenic and HIV-related
Knockaert et al (2003)	Fever of >38°C on several occasions for 3 weeks including a pragmatic investigation period
Bleeker-Rovers et al (2007)	Protracted fever after a structured diagnostic checklist
Vanderschueren et al (2009)	Inclusion of low-grade fever with raised inflammatory markers 'inflammation of unknown origin' (IUO)

In the 55 years since Petersdorf and Beeson's highly cited publication, the speed and availability of investigation has progressed. Clinicians are faced with novel challenges such as complications of immunocompromise secondary to disease-modifying 'biologics' and drugs used in organ transplantation, in HIV infection and its treatment, emerging infections, and nosocomial infections. Efforts have been made to alter the definition of pyrexia of unexplained origin to reflect this, with categorization into groups and updated specifications for investigation (*Table 1*). However, the definition and algorithm for investigation remain ill-defined and have a poor evidence base.

A pragmatic working definition of pyrexia of unexplained origin that may be used involves a 'febrile illness for over 2 weeks with no potentially diagnostic clues, and no diagnosis after a reasonable work-up including three blood cultures and cross-sectional imaging'.

Exploring pyrexia of unexplained origin in modern medicine

Aside from an increase in the pace and range of investigations, there are several other factors inherent in current clinical practice that influence the management of pyrexia of unexplained origin. Justifiably, clinicians' and patients' expectations are higher, resulting in a drive to investigate more comprehensively (Moberly, 2014). Similarly, the challenge of antibiotic resistance

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strengthens the case for tissue biopsy and culture confirmation, in place of empirical treatment, to facilitate accurate diagnoses with antibiotic sensitivity results for infectious aetiologies (Wright and Mackowiak, 2015).

Table 2. Aetiologies of pyrexia of unknown origin

Infections	Tuberculosis
	Atypical presentations of pneumonia and urinary tract infections
	Vascular graft infections
	Intra-abdominal abscess, typically liver or diverticular
	Prostatitis
	Infective endocarditis
	Infection of the bone or joint and/or prosthesis
	Viral infections (Epstein–Barr virus or cytomegalovirus)
	Toxoplasma
	Imported/travel-related fevers that are not commonly seen (brucellosis, Coxiella, enteric fever, Yersinia, Bartonella, leishmaniasis, Histoplasma, blastomycosis, coccidiomycosis)
Inflammation	Crystal arthropathy
	Polyarthritis (rheumatoid arthritis, seronegative spondyloarthropathy, reactive arthritis)
	Adult onset Still's disease
	Haemophagocytic lymphohistiocytosis
	Systemic lupus erythematosus
	Systemic vasculitis
	Thyroiditis
	Autoimmune inherited diseases
Malignancy	Hodgkin and non-Hodgkin lymphoma
	Castleman disease
	Renal cell carcinoma
	Hepatocellular carcinoma
	Acute myeloid leukaemia
	Hairy cell leukaemia
	Blast crisis of chronic myelogenous leukaemia
	Ovarian cancer
	Atrial myxoma
Miscellaneous	Alcoholic hepatitis
	Drug-induced fever
	Habitual hyperthermia
	Factitious fever
Undiagnosed	

Paradoxically, competing demands, relating to cost effectiveness, may limit a clinician's ability to arrange inpatient investigations.

Despite manifold advances in diagnostics, pyrexia of unexplained origin remains a commonly encountered syndrome, and 20–50% of cases are undiagnosed (Vanderschueren et al, 2003; Gaeta et al, 2006; Bleeker-Rovers et al, 2007; Naito et al, 2013). It is frequently cited that pyrexia of unexplained origin accounts for 3% of hospital admissions, although this figure is drawn from data derived over a decade ago (Iikuni et al, 1994; Mourad et al, 2003). More recently, annual UK Hospital Episode Statistics data from 2012–15 suggest that pyrexia of unexplained origin consistently accounts for 0.5% of hospital admissions, approximately 95 000 diagnoses each year with ICD-10 code 50.9 (fever, origin unknown). These data are at risk of ascertainment and reporting bias, and are likely largely to consist of undiagnosed pyrexia of unexplained origin on discharge. These elements of reporting bias are most likely responsible for significant variation in prevalence data between institutions.

The causes of pyrexia of unexplained origins

There are hundreds of causes of pyrexia of unexplained origin, and it is helpful to frame them into broad categories, as displayed in *Table 2* along with common examples. In Petersdorf and Beeson's seminal work in 1961 the frequencies of each of these groups were as follows: 36% infections, 13% inflammation and 19% malignancy (Petersdorf and Beeson, 1961). It has been suggested that the epidemiology is changing, with fewer infections identified (Mourad et al, 2003). This is plausible, as infections are picked up quicker, before the diagnosis of pyrexia of unexplained origin. However, this is not a consistent observation, and may reflect the fact that studies include different proportions of immunocompromised patients, based in contrasting geographical areas with resource implications (Gaeta et al, 2006). Notably, studies frequently restrict their study population to Durack's classical pyrexia of unexplained origin, immunocompetent and community-acquired pyrexia of unexplained origin.

Although many undiagnosed cases are benign and self-limiting, there is a recognized associated mortality, particularly in the first few months (Mourad et al, 2003). Aside from improving diagnostic accuracy in pyrexia of unexplained origin, differentiating the self-limiting from the progressive underlying condition is one of the challenges in choosing the intensity of investigation.

The art of medicine: evaluating a case of pyrexia of unexplained origin

Standardization of investigational algorithms for pyrexia of unexplained origin is a complex task. Aside from issues surrounding case definitions and the limited evidence base guiding investigation choices, there are also geographical differences in aetiology and resources for diagnostic testing. As such, salient questions to consider in the evaluation of

a pyrexia of unexplained origin are provided below, along with case scenarios and current evidence around choice of investigations.

1. Is it a pyrexia of unexplained origin? Has there been a confirmed fever? For a protracted period?

An essential question in the evaluation of a case is whether it is a pyrexia of unexplained origin with a confirmed temperature. This is challenging in the absence of a standardized case definition. However, there is a basic role for a specialist to perform a detailed evaluation based on a comprehensive history, examination and customized minimal set of investigations.

2. Which category of pyrexia of unexplained origin?

Durack and Street's (1991) original article proposed that pyrexia of unexplained origin may be categorized into:

1. Classic
2. Nosocomial
3. HIV-related
4. Neutropaenic.

More recently it has been acknowledged that there is a fifth category, travel-related cases (Wright and Mackowiak, 2015). These are not definitive, but help to provide a framework for further investigation or advice. Immunocompromised patients may have very subtle signs or multiple pathology (Hickam's dictum: 'Patient may have as many diseases as they damn well please'). Furthermore, a positive travel history should warrant an early discussion with a tropical diseases physician to encourage appropriate early investigations, and prevent nosocomial transmission.

3. Are there any 'potentially diagnostic clues'?

Sutton's law 'to go whether the money is' provides sensible advice (Steven and Daniël, 2012). Imaging-targeted biopsy and proactive interaction with histopathology and/or microbiology is advisable (Bleeker-Rovers et al, 2007).

4. Have you missed any common presentations?

Clinical examinations and investigations are rarely 100% sensitive or specific. It important to consider the case in relation to local epidemiology. Parry's maxim 'Why would this person, from this place, present in this way at this time?' has wide-reaching relevance (Mabey, 2013). It may be worth pursuing certain diagnoses even if some investigations are reported as negative, such as a negative interferon gamma release assay in suspected tuberculosis. It is worth referring back to evaluated diagnostic criteria such as the Duke's criteria for endocarditis or the Yamaguchi criteria for adult onset Still's disease.

5. Do you have a detailed overview of the findings to date and is this up-to-date?

Tabulation of fever chart, inflammatory markers, completed and outstanding investigations and response to presumptive treatment can be useful, as is regular re-examination.

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6. Would the patient benefit from a second opinion or referral?

Discussion at a multidisciplinary team meeting enables focussed input from other specialties.

7. How severe is the case and how quickly has it progressed?

Consider the timing of onset, progression and severity of illness in the investigative algorithm. It may be prudent to 'watch and wait'. If, possible, avoid empirical therapy such as antibiotics and steroids that may lead to false negative results (Blockmans et al, 2006; Dumarey et al, 2006).

Case comments

The following three cases highlight salient learning points in the management of pyrexia of unknown origin. They are based loosely on real cases, for illustration, with alterations made to the age and gender and one or two other minor details to ensure the patients are anonymised.

Case 1

Tuberculosis continues to be a major cause of pyrexia of unexplained origin worldwide. It is notoriously difficult to confirm; however, response to empirical treatment should not be considered equivalent to a confirmed diagnosis. The role of positron-emission tomography/computed tomography in pyrexia of unexplained origin is poorly

CASE 1

A 32-year-old Caucasian woman was admitted to hospital with a 3-week history of fevers and sweats. She had no other symptoms or notable history. Examination revealed a mild tachycardia, temperature of 38°C but no other potentially diagnostic clues. She was haemodynamically stable. Full blood count, renal and liver function were normal, C-reactive protein level was 26 mg/litre. A chest radiograph and abdominal ultrasound were unremarkable.

At 5 days, no organisms were grown from three different sets of blood cultures. HIV, hepatitis B and C, Epstein–Barr virus and cytomegalovirus serology were all negative. Transthoracic echocardiography was normal. Computed tomography of the chest revealed a subcarinal node and an endoscopic bronchial ultrasound with fine needle aspirate was inconclusive. She improved marginally without treatment and was discharged for outpatient review.

On return to clinic she reported ongoing symptoms. A positron-emission tomography/computed tomography scan was performed and demonstrated mediastinal fluoro-2-deoxy-D-glucose-avid lymphadenopathy. The endoscopic bronchial ultrasound was repeated, histology revealing caseating granulomas and culture positive for *Mycobacterium tuberculosis*. Review of documentation following the initial lymph node biopsy revealed that this biopsy had been inadequately sampled.

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evidenced, but it is included in current guidelines as a diagnostic modality for pyrexia of unexplained origin when conventional imaging has failed to provide a diagnosis (Royal College of Physicians of London et al, 2016). An unpublished meta-analysis suggests that diagnostic yield in positron-emission tomography/computed tomography is 56% (T Bharucha, A Rutherford, S Skeoch et al, unpublished data, 2016), but this is based on retrospective, observational studies with a high risk of bias. Notably, this statistic does not take into account the yield from previous cross-sectional imaging. This case exemplifies these findings, and highlights the role of questioning negative findings, revisiting findings, repeating investigations and 'going where the money is' with aspiration or biopsy whenever possible. Importantly, positron-emission tomography/computed tomography is unreliable in imaging the brain, heart, gastrointestinal tract and urinary tract.

CASE 2

A 65-year-old man was referred to an infectious diseases clinic by his GP for a 2-month history of fevers. He reported general fatigue and an intermittent cough in the 3 months following his wife's death. He was haemodynamically stable, with no findings on examination. Full blood count, renal function, liver function, C-reactive protein level, bone profile and thyroid function were normal. Computed tomography of the chest-abdomen-pelvis was unremarkable.

At the second outpatient appointment he reported ongoing fevers and sweats, but there were no further findings. He was reassured and asked to keep a fever diary and return. The fever diary suggested high fevers up to 39°C every day so he was admitted for further evaluation. Bloods remained unremarkable. Daily rectal temperatures were recorded and showed no abnormality. He was reassured and discharged to be followed up by his GP with bereavement counselling arranged.

CASE 3

A 42-year-old Turkish woman presented to an emergency department with acute abdominal pain and fevers. She had a past history of recurrent attendances with similar complaints that improved after 24–48 hours. Investigations showed a raised white cell count of $17x10^9$/litre and C-reactive protein level of 190 mg/litre. No organisms were grown from three sets of blood cultures. Chest radiograph, abdominal ultrasound and computed tomography of the chest-abdomen-pelvis were unremarkable. She improved after 24 hours.

On further questioning, she described a family history of similar presentations. She was referred to the auto-inflammatory syndrome clinic. Genetic testing revealed a MEVF gene mutation resulting in a diagnosis of familial Mediterranean fever syndrome. She was started on low dose colchicine, monitored in clinic, and her family members were also tested.

Case 2

A factitious fever is an uncommon 'miscellaneous' cause of a pyrexia of unexplained origin (Aduan et al, 1979). It is important to take the social history into account, and consider a possible role for the patient or the carer in fabricating the fever. Suspicion may be raised in cases of unusual fever patterns, including very high temperatures or loss of diurnal variation, or loss of associated diaphoresis or tachycardia, or rapid defervescence, or normal inflammatory markers. Occasionally, it may be helpful to take a rectal temperature.

Case 3

Familial Mediterranean fever is one of the more common systemic auto-inflammatory syndromes, with an estimated prevalence of 1:1000 Turkish individuals (Lachmann, 2015). Other systemic auto-inflammatory syndromes include tumour necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency, cryopyrin-associated periodic syndrome and Schnitzler's syndrome (Federici et al, 2015). These are rare disorders of innate immunity, and while they are usually diagnosed in childhood, the onset may be delayed. There are evidence-based treatments available such as colchicine for familial Mediterranean fever, and these prevent the chronic complications of amyloidosis, joint and neurological impairment. Systemic auto-inflammatory syndromes present recurrently, often severely, meaning that patients may undergo multiple, unnecessary investigations.

The future: the challenge of research on pyrexia of unexplained origins

Clinicians worldwide continue to encounter patients with pyrexia of unexplained origin, leading to challenging clinical questions regarding appropriate investigations and treatment. Current management of pyrexia of unexplained origin is inconsistent, with a limited evidence base. For example, an abdominal ultrasound is often seen as an essential part of the work-up, but in the absence of deranged liver function tests or localizing symptoms there is minimal yield associated with this test (Chacko and Brar, 2014).

There is a clear need for the standardisation of case definitions and investigative algorithms. However, the management of pyrexia of unexplained origin is as much an art as a science and may perhaps remain as such. Research in the area is fraught with difficulties: small case numbers, restrictive case definitions excluding immunocompromised patients outside of hospital settings, biased case recruitment and results unable to be generalized as a result of geographical variation. Furthermore, the availability of investigations is variable,

there are no gold standard diagnostic tests for comparison, and outcome measures are unconvincing. Currently, there remains minimal evidence to guide the management of pyrexia of unexplained origin and demand for further research in this area.

And when all possible tests are done…

'I often say quite plainly to them, or (more often) to their responsible relatives, "This is a very unsatisfactory state of affairs. Life cannot be lived without small risks. Are you prepared to take a little risk? You have had very exhaustive and expert examinations, and nothing has been found, except this highly nervous state of the patient. I propose, therefore, to stop taking the temperature and to start on a system of gradual and encouraging re-education of these toneless muscles and this toneless nervous system, and see what comes of it. I promise you I will interrupt this programme so soon as something develops which can be definitely treated." That is an attitude which I not uncommonly adopt, and in the cases in regard to which due care has been exercised to exclude organic disease, things do not go wrong. If it be true that the proof of the pudding is in the eating, it must be a sound method, seeing that the results seem to justify the wisdom of it, for most of the cases go straight ahead and get well.' (Horder, 1925) BJHM

KEY POINTS

- Definitions of pyrexia of unknown origin used in clinical practice are evolving, and require standardization for future research.
- Broad categories of pyrexia of unknown origin include classical, nosocomial, neutropaenic, HIV-related and travel-related.
- New diagnostic modalities, especially DNA amplification, host genetic sequencing and nuclear medicine techniques, have lent precision and speed to the diagnostic process.
- There is less emphasis on empirical treatment with antibiotics or steroids as these may hinder diagnostic yield from biopsies or other specimens.
- Numerous questions remain, including the role of a standardized algorithm for testing, and the yield from certain investigations such as fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography.

Conflict of interest: none.

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