INVITED ARTICLES

PYREXIA OF UNKNOWN ORIGIN – APPROACH TO MANAGEMENT

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ABSTRACT

Pyrexia of unknown origin (PUO) remains one of the major diagnostic challenges for the clinician. Although infection, malignancy and collagen vascular disease remain the 3 most important causes of PUO, the relative importance of different disease entities within each of these major categories has changed because of improvements in serodiagnosis, culture techniques and radiologic imaging modalities. A detailed clinical history and meticulous physical examination remain the mainstay of the approach to management of patients with PUO. There is no set of "routine" investigations that patients with PUO should be subjected to. Instead, diagnostic testing should be individualised and guided by abnormalities found on clinical examination and simple laboratory testing. In patients in whom the diagnosis remains obscure in spite of extensive investigations and in whom the disease process is clearly progressive, judicious use of narrow spectrum anti-microbial therapy may be warranted. In the majority of the other patients who remain stable, careful clinical observation for new symptoms and signs are advised in the place of multiple courses of antimicrobials.

Keywords: *pyrexia, fever, infection, malignancy, autoimmune disease*

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INTRODUCTION

"Humanity has but three great enemies; Fever, famine and war; of these by far the greatest, by far the most terrible, is fever"
Sir William Osler, 1849-1919

Fever has been observed and recognised as a cardinal manifestation of disease from the earliest recorded history. The severity of fever was initially sensed and later measured by thermometry from the 1800s. The presence of fever and its pattern were found to be a reliable marker of illness and Wunderlich and Osler documented and emphasised its diagnostic and prognostic value. Fever was considered initially as an indication of infection but later also recognised as an accompaniment of other disease entities including malignancy, autoimmune disease and other multisystem diseases associated with "sterile" inflammation.

Persistent fever without any obvious cause is an uncommon, difficult and frustrating diagnostic problem that often tries the patience of both patient and attending clinician. The causes of prolonged pyrexia of unknown origin have been well described in the literature since the 1930s by Alt and Baker[1], and Hamman and Wainright[2], followed by the classic manuscript of Petersdorf and Beeson in 1961[3] and regularly "updated" by numerous other authors[4-11]. Pyrexia of unknown origin in the 1990s brings new diagnostic challenges with changes in patient and disease profile due to infections related to leisure and travel activities, immunocompromised states, improvements in diagnostic tests including serologic, culture and molecular biologic techniques and radiological imaging studies such as computed tomography, magnetic resonance imaging, echocardiography and radionuclide scans.

Infectious disease physicians are frequently called upon to evaluate patients with PUO. Kazanjian[8] reported that 1.4% of all referrals to an infectious disease physician, fulfilled the criteria for PUO. The aim of this manuscript is to provide a perspective of PUO and hopefully to provide a conceptual framework for management of such patients.

Definition of pyrexia of unknown origin

The definition established by Petersdorf and Beeson in their seminal article published in 1961 on 100 patients continues to be useful today[3]. The criteria selected were illness of more than 3 weeks duration, fever of 38.3°C (101°F) on several occasions and uncertain diagnosis after one week of study in hospital. These criteria were used to eliminate many self limited illnesses including viral infections, drug fever and habitual hyperthermia. The one week stay was to allow for the completion of some laboratory studies that were made to identify the cause of the febrile illness. The first 2 criteria have been retained by almost all other investigators but the improved availability of more rapid diagnostic tests and increased costs of hospital care have questioned the requirement of the week long hospital stay. Durack and Street in 1987[10] suggested that the criteria be changed to 3 days' of hospital stay. Petersdorf in an editorial in 1992[12] acknowledged these changes and suggested that the criterion of 1 week hospitalisation be changed to 1 week of "intelligent and intensive investigations".

Pyrexia of unknown origin occurs in many immunocompromised patients including cancer patients with or without neutropenia, patients who have undergone organ transplantation, patients on immunosuppressive drugs such as those with systemic lupus erythematosus (SLE) and patients with

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Human Immunodeficiency virus (HIV) disease. The causes of fever in these patients are often different from patients with "classical PUO" in that they have more unusual and opportunistic infections as well as a higher incidence of drug fever because of the polypharmacy that most of these patients are exposed to. The management of such patients fall in the domain of the sub-subspecialists and the infectious disease physicians. For example, empiric antibiotics are almost always started on patients with neutropenic fever whereas the converse is true for patients with classical PUO. For the sake of brevity of this article, we will focus on the patients with classical PUO.

Causes of pyrexia of unknown origin

The 3 broad categories of causes of PUO in most published series were infection (30%-40%), malignancy (20%-30%) and collagen vascular disease (10%-15%). The causes that have been reported in 6 major series[3-8] are listed in Table I. Comparison between different series is difficult because differences in geographic factors, referral patterns, experience of investigators, average age of patients, diagnostic strategies (especially as to what constitutes a "routine" test in a patient with obscure fever) all influence the diagnostic categories. Five of the 6 series listed in Table I were from university hospitals[3-7] and the one by Kazanjian[8] was from a community hospital. The varying significance and prevalence of different diseases may reflect the bias in patient population. Of note, there were 2 "pairs" of series from original authors in the Table, Petersdorf et al [1952-'57[3] and 1970-'80[4]] and Barbado et al [1968-'81[5] and 1982-'89[6]]. These paired series help clarify the change in spectrum of disease causing PUO with time. The reasons for this change in spectrum were multifactorial. They reflect improved diagnoses of conditions such as abdominal abscesses because of availability of cross sectional imaging such as ultrasonography and computed tomography (CT), SLE by improved serology, endocarditis by transthoracic and transesophageal echocardiography and improvements in microbiologic culture techniques, to name just a few. These studies have demonstrated that the disease conditions that depend on clinical diagnosis and observation and which at present do not have a specific serologic marker, easily accessible microbiologic culture or which do not lend themselves to easy radiologic studies, will increase in importance.

Infection

The incidence of intra-abdominal abscesses causing PUO has been reported to be decreasing; in one paired series by Barbado et al[5,6], there were no patients with intra-abdominal abscess in the later series[6]. The incidence of hepatobiliary disease has also decreased in importance as a cause of PUO. The reduction of these two conditions reflects the improved abdominal imaging and availability of ultrasonography and CT and also endoscopic retrograde cholangiopancreatography. Similarly, the advent of echocardiography has reduced the importance of infective endocarditis as a cause of PUO. However, we must emphasise that we do not advocate these investigations on a routine basis for patients with PUO. In one report of PUO in which 9 patients were found to have intra-abdominal abscess by ultrasound or CT, 8 out of the 9 patients had a history of recent abdominal surgery and/or appendicitis, cholecystitis, diverticulitis or trauma[8]. It is also recognised that echocardiography is a low yield diagnostic procedure in patients with fever who do not have any symptoms and signs of cardiac illness. Therefore, in patients with PUO, a history suggestive of intra-abdominal surgery or a history of heart disease associated with physical signs of valvular disease are indications for these investigations and not otherwise.

Rheumatic fever has now been rarely reported as a cause of PUO. This reflects decreased incidence of the disease in most developed countries. The likely reasons for this are the

Table I – Final diagnosis in major series of pyrexia of unknown origin.

Diagnostic category	Petersdorf & Beeson '61 ['52-'57] (n=100)	Larson et al '82 ['70-'80] (n=105)	Barbado et al '84 ['68-'81] (n=133)	Barbado et al '92 ['82-'89] (n=85)	Knockaert et al '92 ['80-'89] (n=199)	Kazanjian '92 (n=86)
I. Infection	36	30.4	30.8	10.6	22.6	32.6
a. Abdominal abscess	4	10.4	3	0	2.1	10.5
b. Hepatobiliary disease	7	0.9	1.5	2.3	0.5	2.3
c. Tuberculosis/Mycobacteriosis	11	4.7	11.2	9.4	5	4.7
d. Endocarditis	5	0	1.5	0	1.5	4.7
e. Viral (primarily CMV)	0	3.8	0	0	4	4.7
II. Malignancy	20	31.4	18	28	7	24
a. Lymphoma	6	16.1	12	14.1	1	16.3
b. Other haematologic	2	4.8	0	0	2	2.3
c. Solid tumours	9	10.4	5.3	11.8	4	8.1
III. Collagen vascular disease	15	8.9	12.8	29.4	19.1	16
a. SLE	5	0	0.7	0	0.5	2.3
b. Still's disease	2	3.8	0.7	5.9	3	5.8
c. Temporal arteritis	1	1.9	3	11.8	8.5	1.2
d. Rheumatic fever	6	1	0	0	0	1.2
IV. Granulomatous disease	4	7.6	1.5	4.7	2	5
a. Sarcoidosis	2	1.9	0	0	2	1.2
b. Crohn's disease	0	1.9	0.75	2.4	0	2.3
c. Granulomatous hepatitis	2	3.8	0	0	0	0
V. Drug related fever	1	0	0	0	3	0
VI. Factitious fever	3	2.8	4.5	3.5	1.2	1.2
VII. Miscellaneous	15	8.5	9.7	5.9	14.5	11.6
IX. Undiagnosed	9	16	21.7	15.3	25.6	9

availability of Anti-Streptolysin O Titer (ASOT) and throat cultures and widespread use of antibiotics for pharyngitis. However, clinicians are cautioned that small outbreaks of rheumatic fever have recently been reported in developed countries and continued vigilance against this disease is required.

Tuberculosis remains an elusive diagnosis to make and most of the patients reported in PUO series were more likely to have extra-pulmonary or other cryptic forms of tuberculosis[4,8]. Viral infections especially Cytomegalovirus may present in a nonspecific fashion with prolonged fever. Acute HIV infection and chronic illness due to HIV or its related opportunistic infections are important differential diagnoses and because this infection is increasing worldwide, all clinicians should consider this diagnosis in patients who have multiple sexual partners or other high risk behaviour. Just as epidemiological factors need to be considered, geographic prevalence should influence the degree of diagnostic index. Melioidosis is endemic in South East Asia and presents with protean manifestations. The patients with hepatosplenic abscesses due to melioidosis often present with nonspecific signs and symptoms and this condition must be considered an important differential in Singapore.

Malignancy

Lymphoma, in particular the non-Hodgkin's type, may present only with "B" symptoms without peripheral adenopathy. Lymphoma has been reported in one series as the single most common cause of PUO[8]. Other haematologic malignancies that have proved to be elusive in diagnosis include acute aleukemic leukaemia[4,7] and the plasma cell dyscrasias such as multiple myeloma. For the "solid" tumours, the intraluminal tumours such as colonic carcinoma need to be considered[7].

Collagen vascular disease

The incidence of collagen vascular disease causing PUO appears to be increasing. Because of improved serodiagnosis, SLE as a cause has been reported to be decreasing[6-8] whereas disease entities that present clinically in a nonspecific fashion and which do not have any definitive serologic marker such as adult Still's disease and temporal arteritis/polymyalgia rheumatica, appear to be increasing in importance as causes of PUO. In two recent series from university hospitals, the "occult form" of temporal arteritis was the single most common cause of PUO[6,7]. Petersdorf astutely states that "a different spectrum of diseases causing PUO will emerge when rapid serologic markers are found for polymyalgia rheumatica"[12].

Miscellaneous causes of PUO

Unusual and uncommon causes of PUO such as Crohn's disease, de Quervain's thyroiditis, familial Mediterranean fever, sarcoidosis, Reiter's syndrome, pulmonary embolism, intra-abdominal haematoma, endocrine disorders including thyrotoxicosis and phaechromocytoma, unusual infections such as Brucellosis, rickettsiosis and deep seated fungal infections have all been reported in these PUO series[3-8]. In the appropriate patient, "central fever", autonomic dysreflexia, "spinal" fever should be considered. The diseases listed here are by no means exhaustive.

"New causes" of PUO

Lyme's borreliosis is an infection caused by the spirochete, *Borrelia burgdoferi* with the tick as the insect vector. The clinical presentation may be highly variable with erythema chronicum migrans in the acute phase, chronic meningitis and seronegative arthritis occurring during the chronic phase of the illness. To the best of our knowledge, no patient has acquired Lyme's borreliosis in Singapore although the vector is apparently present in Singapore. The potential of developing infection due to this pathogen remains a distinct possibility and we await reports of the first local case.

Chronic fatigue syndrome may present initially as PUO but the temperature rarely exceeds 38.3°C. This disease may be triggered by a viral infection or a virus like syndrome[13] and then continue with significant psychomotor impairment as a major manifestation. Its relation to an endogenous depressive illness and the possible links to other illness reflect our poor understanding of this syndrome which fortunately is uncommon in the Asian population but plagues patients in the Western hemisphere.

Patients with idiopathic granulomatosis, an entity recently reported in 15 patients from the Mayo Clinic, present with prolonged unexplained fever[14]. Routine haematological and biochemical tests revealed nonspecific abnormalities, all cultures are sterile and widespread granulomas (not caused by any known disease such as tuberculosis, sarcoid or drugs etc.) were detected on biopsy of liver, lymph node, spleen and bone marrow.

Habitual hyperthermia and factitious fever

The term habitual hyperthermia is considered a misnomer. It describes patients in whom the diurnal variation in temperature is more pronounced. The normal body temperature falls within a range of 36-38°C with the temperature lowest in the early morning or upon awakening and the highest in the late afternoon and early evening. The typical patient is usually a young woman in her 20s or 30s who is otherwise well except for late afternoon and evening temperatures that have been carefully recorded. Temperatures rarely exceed 38.3°C and these patients are usually excluded from most series of PUO.

Falsely elevated oral temperatures may result from smoking, eating/drinking hot food, vigorous gum chewing or in those predisposed to manufacturing illness. We recently suspected the presence of factitious fever in a female health care worker who had temperature spikes of up to 39.5°C without any associated symptoms. There was a pulse-temperature dissociation. Unscheduled and unannounced monitoring of her temperature in hospital repeatedly revealed temperatures within the normal range. Axillary and rectal temperatures instead of conventional oral temperature may preclude errors in temperature reading due to ingestion of hot liquids and "exothermic substances". In the patient described, we were unable to obtain any definitive proof of her falsifying her temperature. Her presentation is the classic description of patients with factitious fever.

Undiagnosed

Despite investigations, a proportion (9-25%) of otherwise well patients will remain undiagnosed and continue to perplex and frustrate the clinician[3 8]. Series from university referral centre may have a higher proportion of undiagnosed patients[7] as opposed to those from community hospitals[8] but this line of reasoning was disputed by Petersdorf[12]. In some cases, the saying "you find what you look for" may hold true.

What to do when the fever does not go away?

Retake the history and conduct a complete physical examination. Fever that presents acutely with local signs and symptoms rarely remains undiagnosed. This category of patients is not the subject of discussion outlined in this manuscript. For patients who are otherwise reasonably well but persist to have fever, obtaining a detailed history on any symptoms and signs referable to all organ systems is mandatory. In addition, the clinicians must obtain a travel history, contact with animals and pets, and any leisure

activities particularly outdoor pursuits that may predispose to unusual infections. From these 2 basic steps, we can move on to investigate the patient based on the clinical information available.

Initial investigations to be ordered

There is no specific set of investigations that all patients with PUO should routinely be subjected to. Diagnostic testing must be guided by a detailed history and physical investigations. If there are no signs of symptoms referable to any organ system, some routine investigations are warranted. Full blood count (FBC), erythrocyte sedimentation rate (ESR), renal and liver function panel, aerobic and anaerobic blood and urine cultures, chest radiograph and a urine microscopy would usually be ordered. In the appropriate patient, investigations to rule out autoimmune disease (antinuclear factor, anti-DS DNA, rheumatoid factor, complement levels: C3, C4 and CH_{50}) and malignancy (stool for occult blood, relevant cytologies and biopsies, lactic dehydrogenase, ß2 microglobulin, α-fetoprotein, CA19-9, CA125 and prostate specific antigen levels) should also be considered where relevant.

What to tell the patient?

Be honest. If the patient has signs and symptoms referable to a specific organ system, your chances of arriving at a diagnosis within the week is good. In contrast, if the patient presents only with nonspecific symptoms with an essentially normal physical examination, explain your management strategy to the patient. In addition, patients who are evaluated as outpatients are advised to keep a chart of their temperature at least 4 times a day and also to record any symptoms that may develop at or around the time of elevated temperatures.

Do I need to start antibiotics?

In published series as well as by our limited experience, the vast majority of patients with classical PUO suffer more harm and delay in diagnosis from the use of empiric antibiotics than when careful monitoring and intelligent investigations alone were employed. The immediate mortality of such patients is low but they may subsequently be diagnosed as having an underlying illness that may ultimately prove fatal. If the patient has an acute or subacute illness that is progressive and is sufficiently ill to warrant antimicrobial therapy, it is advised that the patient be admitted to a general hospital where investigations may be emergently performed especially microbiologic investigations prior to use of empiric antibiotics. The choice of antimicrobial therapy in these patients must be clearly targeted at specific disease entities rather than a regimen of 4-6 antibiotics which will cover all possible infections. The clinician should determine what the most likely aetiologic agent causing the infection and fever is, perform the relevant investigations and use a narrow spectrum antimicrobial regimen specifically for the organism suspected to be the cause of the illness.

If fever continues.....

The time period before more extensive and expensive investigations are used depends on the clinical condition of the patient, the clinical progress and patient tolerability of his/her illness. Further or repeat investigations should be focussed and target symptoms and signs detected following a repeat clinical evaluation of the patient. Many patients are categorised as having PUO because an obvious clue is overlooked, disregarded or rejected. To repeat the obvious, go through the clinical history and physical examination with a fine toothed comb. This requires the clinician to work much harder and the problem may be compounded by the patient who has been unwell for several weeks, is now extremely anxious and who has chronic symptoms that are often difficult to differentiate from the current illness. A typical example is a patient with PUO who has had a history of "gastritis" in the past and whose abdominal discomfort has recurred in a similar but not identical fashion. A oesophagogastroduodenoscopy may be required despite the fact that the patient is known to have peptic ulcer disease for the past 10 years. The working guidelines that should be followed must focus on an atypical presentation of a common illness rather than a typical presentation of an uncommon disease.

When to proceed to more sophisticated imaging studies or more invasive tests?

As there is an unending list of causes of PUO and there are multiple work-ups available, one must plan a logical and individualised approach for the patient. The rule of thumb is to begin with simple, inexpensive and less invasive laboratory tests before progressing to more detailed, complex and more invasive investigations. In general, it would be reasonable to say that the more stable the patient's condition is, the more directed and deliberate the pace; the sicker the patient is, the more rapid should the progression to invasive interventions and even empiric therapy (eg anti-tuberculous treatment, infective endocarditis treatment).

A repeat of some of the basic investigations such as FBC, ESR, renal and liver panels, blood, urine and sputum cultures, urinalysis, CXR may be required. Further investigations should be directed by clinical evaluation and clues; such as collagen workup, serology screens viz, Venereal Disease Research Laboratory, ASOT, Cytomegalovirus and Ebstein Barr Virus serologies, viral cultures of urine and buffy coat, febrile agglutinins such as *Salmonella, Brucella* serology, Widal-Weil Felix test.

The cue to perform more 'high tech' investigations should be taken from symptoms referrable to a system and not be ordered blindly. Computed tomography of the abdomen and pelvis should be considered in patients with abdominal symptoms, past history of abdominal surgery, intra-abdominal infections such as cholecystits and diverticulitis and when the patient is suspected to have melioidosis. Abnormal liver panel may be considered as an indication to request for radiologic imaging of the abdomen. Similarly, endoscopy or barium studies are indicated in patients with gastrointestinal symptoms. Bone marrow aspirate and trephine biopsy studies are useful when tissue for histology and culture studies are required. The advent of lysis centrifugation techniques for blood culture may subsequently obviate the need for bone marrow aspirate cultures. In an elderly patient in whom extensive investigations have not yielded any specific diagnosis, it has been suggested that a temporal artery biopsy be considered. With improved imaging studies of the abdomen, exploratory laparotomy/laparoscopy is usually reserved for patients in whom abnormalities are present on CT scan. Liver biopsy is a valuable investigation in the workup for PUO as it yields histologic and microbiologic clues to disease process and it is a relatively safe procedure when performed by an experienced clinician.

Does the patient need to be hospitalised?

The majority of patients may be investigated and monitored as outpatients[10,12]. The need for hospitalisation depends on the following factors: tempo of the illness, rapidity of investigations required and the need to confirm the patient's symptoms with objective signs. The tempo of illness and the patient's clinical state are the most important determinants for hospitalisation. For patients who have a subacute/chronic disease process that has displayed inexorable progression, admission to hospital is

generally advised to allow for closer clinical monitoring, urgent investigations and consideration for empiric antibiotic therapy. In the rare instances when habitual hyperthermia or factitious fever are suspected, admission to hospital and monitoring of patient's signs may be required to confirm the presence of fever and its magnitude. Pulse temperature dissociation (Faget's sign) is another important observation for these 2 conditions as well as for infections associated with many intracellular pathogens.

When to use adjunctive therapy?

In a patient with a presumptive diagnosis of PUO, it is often important to establish that the patient indeed has a fever. Antipyretic agents are therefore best avoided until the fever pattern has been determined. For patients in whom no diagnosis can be found in spite of a comprehensive workup, adjunctive therapy to reduce symptoms may be instituted with caution, balancing carefully the risks and benefits of such therapy. In general, there exists very few guidelines for the management of patients with prolonged fever in whom no diagnosis is found and whose condition remains stable for weeks and even months. Many series have shown that such patients have good prognosis and generally low mortality. Re-evaluation at monthly intervals would be the prudent approach since signs and symptoms evolve or may become apparent only after prolonged periods of observation. If the fever is debilitating, simple anti-pyretics such as aspirin or acetoaminophen may be administered. Non-steroidal anti-inflammatory agents with their prostaglandin synthetase inhibitor activity, are alternative fever lysis agents as there has been experimental evidence that the negative nitrogen balance seen in chronic fevers may be partially reversed by their use. Readers may be interested to know that certain NSAIDS such as naproxen have been used to differentiate between malignant fever and fever due to infection[15]. In one study, cancer patients with malignant fever were more likely to have resolution of fever upon ingestion of naproxen as compared to patients who had underlying infection[15].

When symptoms of fever are particularly crippling and not responsive to NSAIDS and other antipyretics, the use of empiric steroids may be cautiously considered in an attempt to ameliorate these symptoms[16]. Steroids should only be used in patients in whom all possible infections have been excluded. The clinician must weigh the need for fever resolution with steroids against the potential harmful effects of steroids in a possible undiagnosed infection. We caution against the empiric use of steroids in a patient with undiagnosed fever.

The outcome of patients with PUO

The most favourable outcome for patients with PUO were for individuals who had infection[8]. In contrast, patients with malignancy had the highest mortality and those with autoimmune/multisystem disease had the most morbidity[8]. It would be unusual and would obviously reflect poorly on any clinician who has significant patient mortality from an undiagnosed PUO.

What to do with a patient with persistent fever after extensive investigations and therapeutic manoeuvres and who continues to look relatively well?

Regular and careful observation. The number of patients who remained undiagnosed after an initial comprehensive diagnostic workup constitute 9%-25% of any published PUO series[3-8]. These patients need to be regularly reviewed and any new symptom or clinical progression will require meticulous evaluation and possible further investigations. In patients who were subsequently found to have lymphoma, the development of adenopathy either peripheral or on abdominal CT scan after months of clinical observation for PUO is well described in the literature and also reflects our own clinical experience of two recent cases which were eventually diagnosed to have T cell lymphoma involving the paranasal space and gastrointestinal tract respectively. It is unclear if such patients would have been diagnosed earlier by regular whole body imaging rather than regular clinical review. Our own approach is not to depend upon regular "blind" investigations. Larson et al describe this approach most succinctly, "there is no substitute for observing the patient, talking to him, and thinking about him"[4].

CONCLUSION

Infection, malignancy and multisystem autoimmune disease remain the three most important causes of PUO but the list of possible causes of PUO is legion and enlarges constantly. When the diagnosis remains obscure despite a comprehensive workup, such patients need regular reviews, reassessment and observation for development of overt disease. The approach to a patient with PUO should not be an onslaught of diagnostic tests, most of which are invasive, time consuming and expensive; nor should the patient be choked with the newest and most expensive antimicrobial. What the patient needs is your patience and diagnostic skills to reevaluate the clinical history and physical examination and look for subtle clues.

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