EDITORIAL

FEVER OF UNKNOWN ORIGIN

R E Van Scoy

SINGAPORE MED J 1993; Vol 34: 373-375

Fever of Unknown Origin (FUO), also known as Pyrexia of Unknown Origin, is defined by three very important criteria:

1. The patient must actually have documented fever of over 37.8°C by mouth or 38.3°C by rectum on several occasions,
2. for a period of over 3 weeks duration,
3. with no diagnosis after one week of appropriate studies.

The first criterion is important because many patients are unaware that the normal range of temperature is as high as 37.8°C or 100°F by mouth or 38.3°C or 101°F by rectum. In some practices, it is common to see patients who do not feel well, have loss of energy, multiple musculoskeletal complaints and are generally not happy. They may say their usual temperature is a degree below normal and that 99.0°F or 37.3°C or so is a fever for them. These patients do not have FUO and should not be subjected to an extensive FUO investigation.

The second criterion prevents an extensive FUO evaluation in transient, relatively harmless disorders that last less than 3 weeks.

The third criterion excludes relatively easily diagnosed cases such as endocarditis when the patient has not received prior antimicrobial agents, obvious metastatic liver disease, and conspicuous pulmonary tuberculosis.

The patient and nearest relative or friend are advised of the importance of testing and examinations as well as the likely one to two weeks or longer needed for such evaluations. In as many as thirty percent of cases, no aetiology is found during the first FUO investigation. The patient may be reassured that the prognosis is usually quite good in such cases if a careful examination has been performed. The patient and relative are not usually pleased to hear this information. However, it is more advantageous to so advise them at the beginning of the FUO evaluation, than several days later when it may be interpreted as an excuse for failure to find an answer.

The approach to the differential diagnosis of FUO is a careful history and physical examination followed by appropriate tests. It is often helpful to repeat the history and physical examination for details or findings not obvious at the first review. The prudent selection of tests and the order in which they are performed requires some orientation to the differential diagnosis. The five major aetiology categories of FUO are:[1,2]

Infectious diseases
Tumours
Connective tissue disease
Factitial disorders
Miscellaneous causes

These categories are very large. It is helpful to discuss each category to limit the differential diagnosis to more manageable dimensions.

Infections may be considered by a compulsive review of systems as well as organism class. Examples considered in the review of systems include endocarditis in cardiovascular system, diverticulitis with abscess, liver abscess, emphyema of the gall bladder in the gastrointestinal system review. Endocarditis certainly may cause fever lasting over three weeks. In addition the diagnosis may not be made in the first week of study as a result of previous use of antimicrobial agents or fastidious organisms such as nutritionally deficient streptococci and the HACEK group. The latter includes *Hemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikonella*, and *Kingella* species. Abdominal infections, including those listed above are particularly prone to escape detection with one week of study in those over the age of 65 years as their symptoms and physical findings may be blunted and not distinctive. Organism class review is equally extensive. The following general comments refer to patients seen in the USA and are not meant to be all-encompassing.

The viral infection most likely to cause FUO is cytomegalovirus. The usual clinical picture is relatively well tolerated fever, hepatosplenomegaly, and atypical lymphocytes on peripheral blood smear. Patient's appetite for a hamburger or pizza may remain intact as opposed to those with a bacteremia or abscess. Other viral infections are much less likely to cause fever for longer than three weeks or go undetected after one week of study. While numerous examples of chronic E. B. virus infection exist, marked abnormalities in physical examination and laboratory tests distinguish those conditions from the "chronic fatigue syndrome" whose aetiologies remain unknown. As a result, E. B. virus is a rare cause of FUO. Human immunodeficiency virus (HIV) and hepatitis B virus when associated with periarteritis may present as FUO.

Bacterial infections are usually discovered in the compulsive review of systems. However, some bacteria may not be considered during that process and deserve mention. They include: *Salmonella typhosa*, *Brucella*, *Listeria monocytogenes*, *Legionella*, *Neisseria meningitidis* when associated with chronic meningococcemia, and occasionally systemic infection with *Neisseria gonorrhea*. In South East Asia and those from that area, *Melioidosis* deserves serious consideration.

Mycobacterium tuberculosis is a well-known cause of FUO. Miliary tuberculosis may be most difficult to diagnose early because 50-60% of cases may have a negative PPD and the initial chest X-ray may be unremarkable. The past history including history of a positive PPD, family history, and travel or residence history are important clues. A positive response should raise the suspicion of tuberculosis to the level of rather intense investigation and culturing often required for diagnosis. Mycobacteria other than tuberculosis (MOTT) may cause FUO in AIDS cases. Rarely, disseminated MOTT may cause FUO in patients with cytopenias.

Histoplasmosis is the most common fungal cause of FUO. Bone marrow examination and culture in addition to blood cultures may be helpful. Positive serologic tests may either

Mayo Clinic and Mayo Foundation
Rochester, MN 55905
United States of America

R E Van Scoy, MD
Consultant, Infectious Disease and Internal Medicine

raise the suspicion or essentially document the diagnosis depending on the titers and number of immunodiffusion bands present. Coccidioidomycosis may present as FUO, but other fungi are uncommon causes.

Parasitic diseases except for toxoplasmosis and malaria are uncommon to rare causes of FUO in non AIDS patients. If the patient has been in an area endemic for malaria in recent years, three thick and thin smears on separate days are indicated regardless of whether prophylactic antimalarial drugs were taken.

Syphilis is a more difficult disease in AIDS patients. Leptospirosis is rare in the USA, and lyme disease is both over diagnosed and missed, but none of these spirochetal diseases is more than rarely a cause of FUO.

Rickettsial disorders other than Q fever are very unlikely to cause FUO in the United States except in those who have travelled to endemic areas. Q fever causing FUO most commonly presents as granulomatous hepatitis or rarely as culture negative endocarditis. Serologic tests are simple and very helpful.

Chlamydial infections in the form of psittacosis or ornithosis should be included in the differential diagnosis when significant exposure to fowl has occurred.

Tumours, most commonly lymphoma, are common causes of FUO. Pel Ebstein fever pattern may occur for years before the lymphoma is evident. Curable colon and renal tumours as well as others are possible. Myxoma may mimic endocarditis. The history and physical examination are again vital. Family history of colon cancer, localised pain and tenderness, palpable lymph nodes, other masses or organs may quickly lead to diagnosis and treament, saving extensive testing and discomfort.

Connective tissue disorders producing FUO are almost always either one of the vasculitis entities or adult Still's disease. The vasculitis group includes cranial arteritis (giant cell arteritis, temporal arteritis), periarteritis nodosa, Churg-Strauss granulomatosis, Wegener's granulomatosis. Takayasu's arteritis and others. History of headache, jaw claudication, cough, mononeuritis multiplex, nasal or ear symptoms or ischemic disorders is meaningful. Absent pulses, abnormalities of the nose or ears, abnormalities of the temporal arteries, bruits, and skin infarcts are major clues to vasculitis.

Adult Still's disease is a very difficult disorder to establish. Usually it occurs in the young, under 40 years. The patients appear toxic with high spiking fever and no localising findings. Later an evanescent rash may appear, particularly at the height of the fever or after a hot shower. Aortic murmurs and joint effusions, especially in the knee may be noted. The white blood count may be elevated. The ferritin may be quite high. However, the diagnosis remains one of exclusion.

Usually, lupus or rheumatoid arthritis that causes fever longer than 3 weeks is readily diagnosed within a week of study. Therefore, these conditions are not common causes of FUO. Dermatomyositis also does not commonly present as FUO. It may, however, when associated with a tumour or in the rare syndrome of dermatomyositis or polymyositis caused by Enterovirus infection in patients with hypogammaglobulinemia.

Scleroderma, for practical purposes, does not present as FUO. Factitial disorders are very difficult to document and treat.[3] The patients are often quite skillful at deception and manipulation. Two general types are known. Alteration of the thermometer type is vanishing in institutions where mercury thermometers are no longer used. When such a case is suspected, the diagnosis may frequently be confirmed by the "factitial opportunity test". The mercury thermometer is carefully shaken to lower than normal body temperature and then placed in the patient's mouth. The patient is advised that the examiner will be gone for 5 to 10 minutes and the door is closed. Others are advised to stay out of the room. Upon returning, if the thermometer has an abnormally high reading, it is again shaken to below normal body temperature and then held in the mouth of the patient by the examiner for at least 3 minutes. If a significant discrepancy between the two readings occurs, the diagnosis is strongly supported if not confirmed.

More common is the factitial disorder where the patient induces disease, such as injecting foreign substances. Examples of such injections include hand lotion into the knee joint, pure culture of *Staphylococcus aureus* intravenously, ink subcutaneously, faeces, saliva and urine injected in various locations etc. These patients present with organic disease, positive physical findings, abnormal laboratory tests, and frequently positive cultures. The major clues to suspect this diagnosis are:

1. The clinical picture does not fit that of any natural organic disease.
2. The patient often has a medical profession association, for example a student nurse, nurses aide, nursing station secretary, pharmacy employee.
3. The patient may have had other medical illnesses that did not fit any known disease pattern.
4. The patient may be quite manipulative with considerable secondary gain.

There are numerous disorders that have been reported to cause FUO that do not fit into the above categories. A few of the more prominent of these miscellaneous causes are drug fever[4], inflammatory bowel disease, multiple pulmonary emboli, thrombophlebitis, granulomatous disease[5] of unknown aetiology including but not limited to sarcoidosis and granulomatous thyroiditis, alcoholic hepatitis[6], cat scratch disease, myeloproliferative disorders, central nervous system disorders, Whipple's disease. Again, the history and physical examination are key in the differential diagnosis. The fecal leucocyte test is a relatively inexpensive test that may give a strong clue to inflammatory bowel disease.

The actual investigation of a patient with FUO is beyond the scope of this editorial. The approach should be guided by the results of the history, physical examination and baseline laboratory tests. In patients over 50 with high sedimentation rate and jaw claudication, generous temporal artery biopsy is indicated. CT scan of the abdomen through the pelvis with and without intravenous and oral contrast material is an excellent screening test early in the FUO workup if no clues lead to specific sites of diagnoses. The history and physical examination should be periodically repeated.

Appropriate cultures and serologic tests, renal X-ray of kidneys are not seen well on CT scan, gastrointestinal X-rays and either gallium or indium scans may be helpful. Focussing on areas of localised pain is often rewarded with a diagnosis.

If after careful and extensive testing no diagnosis is made, it may be indicated to observe the patient for a month. The patient is instructed not to take any antimicrobial agents and to return in one month for reevaluation. The patient should return earlier if the condition worsens or new symptoms emerge.

Infectious disease specialists are particularly adept at the FUO differential diagnosis. They are likely to save considerable time, expenses and discomfort if consulted very early in the evaluation.

References

1. Van Scoy RE. Fever, and fever of unknown origin. In: Hoeprich PD, Jordon MC, eds. Infectious disease, Fifth Edition. Philadelphia, Pennsylvania, USA: JP Lippincott: In press.

2. Knockaert DC. Fever of unknown origin, a literature survey. Acta Clinica Belgica 1992; 47:42-57.
3. Aduan RP, Fauci AS, Dale DC, Herzberg JH, Wolff SM. Factitious fever and self induced infection: A report of 32 cases and review of the literature. Ann Intern Med 1979; 90:230-42.
4. Mackowiak PA, LeMaistre CF. Drug fever: A critical appraisal of conventional concepts. Ann Intern Med 1987; 106:728.
5. Telenti A, Hermans PE. Idiopathic granulomatosis manifesting as fever of unknown origin. Mayo Clin Proc 1989; 64:44-50.
6. Gleckman R, Crowley M, Esposito A. Fever of unknown origin : A view from the community hospital. Am J Med Sci 1977; 274:21-5.