

# Infectious diseases

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## Fever of unknown origin

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### Definitions

#### Fever

The definition of fever is:

a state of elevated core temperature often, but not necessarily, part of the defensive resistance of multicellular organisms (host) to the invasion of live (microorganisms) or inanimate matter recognised as pathogenic or alien by the host.<sup>1</sup>

The term 'pyrexia' is often used synonymously with fever in the UK. Fever should be distinguished from hyperthermia, which is an unregulated rise in body temperature due to a failure of temperature homeostasis.<sup>2</sup> Over 100 years ago Wunderlich recorded multiple temperature measurements on around 25,000 people. He defined normal body temperature as 37°C and suggested that the upper limit of the normal range should be regarded as 38°C.<sup>3</sup> This has formed the basis for subsequent definitions of fever.

#### Fever of unknown origin

Petersdorf and Beeson provided the classic definition of 'fever of unknown origin' (FUO) as a prolonged febrile ill-

ness of at least three weeks' duration, with repeated temperature measurements of 38.3°C or higher, that defies diagnosis after one week of hospital inpatient evaluation.<sup>4</sup> This has subsequently been modified to remove the requirement that investigations are performed in the inpatient setting because most patients can be evaluated as outpatients.

One problem with the definition of FUO is that it does not specify which investigations should have been performed prior to stating that a patient fulfils the definition. This is probably responsible for many of the reported differences in the frequency of FUO attrib-

uted to infection, neoplasm, collagen vascular disease and miscellaneous causes. Arnow and Flaherty have suggested a minimum set of investigations to be performed prior to so defining a patient (Table 1).<sup>5</sup> Adoption of these criteria is recommended to attempt to establish greater comparability between future publications on FUO.

It has been suggested that FUO can be subclassified into four different types:

- classic FUO
- nosocomial FUO
- immune-deficient FUO
- HIV-related FUO.

Only the definition of classic FUO specifies that the patient must have had fevers for at least three weeks.<sup>6</sup> This may potentially cause confusion; it is probably preferable to restrict the term FUO to those cases where FUO has been present for at least three weeks and to exclude HIV and immune deficiency. Unfortunately, many clinicians use the term loosely to include any fever for which a cause has not been found. This should be strongly discouraged because the most likely causes of short-term fevers which have not been thoroughly

**Table 1. Minimum investigations which should have been performed without a diagnosis being established prior to qualifying as fever of unknown origin.**<sup>5</sup> Reproduced from the *Lancet* with permission from Elsevier.

- Comprehensive history
- Repeated physical examination
- Full blood count
- Routine biochemical profile
- Urinalysis and microscopic examination
- Chest X-ray
- Erythrocyte sedimentation rate (and/or C-reactive protein)
- Antinuclear antibodies
- Rheumatoid factor
- Angiotensin-converting enzyme
- Routine blood cultures (three sets) while not receiving antibiotics
- Cytomegalovirus IgM antibodies or virus detection in blood
- Heterophile antibody test in children and young adults
- Mantoux skin test
- CT scan of abdomen (or radionuclide scan)
- HIV antibody test
- Further evaluation of any abnormalities detected by the above tests

CT = computed tomography; Ig = immunoglobulin.

investigated are very different from those of FUO.

**Causes of fever of unknown origin**

The causes of FUO in Europe and the USA, reviewed by Armstrong and Kazanjian<sup>7</sup> in 14 papers published since 1930 (Table 2), were found to be:

- infection: 30% of cases
- neoplasms: 18%
- collagen vascular diseases: 12%
- miscellaneous causes: 14%
- undiagnosed: 26%.

There is substantial variation between the different series. In particular, collagen vascular diseases were less frequent causes of FUO in earlier case series than presently. In resource poor countries FUO is more frequently due to infections than in established market economies.<sup>6</sup> This may partly represent differences in the geographic and temporal distribution of diseases, but is also explained by

the thoroughness of the investigations performed prior to classifying a patient as having FUO and the diagnostic tests subsequently available to investigate it. For example, the availability of highly sensitive blood culture techniques and high quality echocardiography means that bacterial endocarditis is now a less common cause of FUO because the condition can be diagnosed relatively easily and is therefore unlikely to meet the FUO criteria.

*Children and young adults*

The relative likelihood of FUO being due to specific causes is related to the age of the patient. In children, infections are the most common cause. Jacobs and Schutze found that 64 of 164 children with FUO had infections including Epstein-Barr virus infection, osteomyelitis, bartonellosis and urinary tract infections.<sup>8</sup> Many children with FUO recover without a diagnosis ever being established. A cause is not found in over 40% of children

under 18 years with FUO compared with less than 5% for adults over 65 years.<sup>9</sup> However, joint disease in children with FUO suggests a serious underlying disorder such as connective tissue disease (CTD), endocarditis or leukaemia.<sup>10</sup> Still's disease, an important cause of FUO in children, can also affect young adults and is a condition often neglected during the search for a cause. Malignancy is a relatively uncommon cause in children<sup>8</sup> and young adults,<sup>11</sup> but lymphoma is a potential diagnosis which is important to exclude because delay in diagnosis may adversely affect prognosis.

*The elderly*

Haematologic malignancies and solid tumours are more common causes of FUO in elderly patients than in younger adults.<sup>11,12</sup> Infections and CTDs are also frequent causes in the elderly. Temporal arteritis and polymyalgia rheumatica are particularly common in this age group. Symptoms of temporal arteritis may be

**Key Points**

The term 'fever of unknown origin' (FUO) should be used only if the patient has had a febrile illness for more than three weeks and a thorough history, examination and appropriate investigations have failed to elucidate the cause

Careful history taking and repeated, thorough physical examinations are more likely to establish the diagnosis than a 'scatter-gun approach' to performing complex investigations

FUO can be caused by a wide range of conditions including infections, connective tissue diseases and malignancies

The older the patient the more likely malignancy is to be the cause of FUO

A therapeutic trial of empirical antibiotics is usually inappropriate

**KEY WORDS:** antipyretic drugs, body temperature, fever, fever of unknown origin, pyrexia

**Table 2. Causes of fever of unknown origin in Europe and the USA and their relative frequency reported in the literature (1930–97). Adapted from Reference 7.**

Country and year of publication	Patients with attributed diagnosis (%)				
	Infection	Neoplasm	Collagen vascular disease	Miscellaneous	Undiagnosed
USA 1930	24	11	0	2	63
USA 1936	59	22	0	0	19
USA 1939	64	24	0	12	0
Sweden 1953	24	16	6	6	49
USA 1959	21	30	0	29	20
USA 1961*	36	19	15	23	7
Finland 1962	19	6	6	0	69
USA 1963	20	18	13	10	38
Sweden 1966	13	32	3	7	45
USA 1973	40	20	15	17	8
USA 1982	30	31	9	17	12
Belgium 1992	23	7	21	24	26
USA 1992	33	24	21	13	9
Netherlands 1997	26	13	20	12	30
<b>Total</b>	<b>30</b>	<b>18</b>	<b>12</b>	<b>14</b>	<b>26</b>

\* The classic paper of Petersdorf and Beeson.<sup>4</sup>

**Table 3. Clues to the cause of a fever of unknown origin suggested by the history.** Adapted from Reference 13.

<b>Medication or exposure to toxic substances</b>	Drug fever Fume fever	<b>Recent history of stroke</b>	Culture-negative endocarditis Takayasu arteritis Polyarteritis nodosa
<b>History of tick bite</b>	Relapsing fever Lyme disease	<b>Cough with sputum production</b>	Tuberculosis Coxiella infection Psittacosis Typhoid Lung cancer Acute rheumatic fever
<b>Contact with animals or birds</b>	Psittacosis Leptospirosis Brucellosis Toxoplasmosis Bartonellosis Coxiella infection Rat-bite fever	<b>Visual disturbance or eye pain</b>	Temporal arteritis Culture-negative endocarditis Brain abscess Takayasu arteritis
<b>Complaint of myalgia</b>	Trichinosis Culture-negative endocarditis Polyarteritis nodosa Rheumatoid arthritis Familial Mediterranean fever Polymyositis	<b>Complaint of fatigue</b>	Carcinoma Lymphoma Cytomegalovirus infection Typhoid Systemic lupus erythematosus Rheumatoid arthritis Toxoplasmosis
<b>Complaint of headache</b>	Relapsing fever Rat-bite fever Chronic meningoenzephalitis Malaria Brucellosis CNS malignancy	<b>Abdominal pain</b>	Polyarteritis nodosa Familial Mediterranean fever Relapsing fever
<b>Cognitive function slowing/confusion</b>	Sarcoid meningitis Tuberculous meningitis Vertebral osteomyelitis Cryptococcal meningitis Carcinomatous meningitis CNS malignancy Brucellosis Typhoid HIV infection	<b>Complaint of back pain</b>	Brucellosis Culture-negative endocarditis
		<b>Complaint of neck pain</b>	Subacute thyroiditis Adult Still's disease Temporal arteritis (angle of jaw) Mastoiditis Septic jugular phlebitis

CNS = central nervous system.

non-specific, such as lethargy and general malaise, which may result in diagnostic delay and risk of blindness from retinal artery occlusion.

## Approach to diagnosis

The investigations to be performed prior to defining a patient as having FUO are listed in Table 1. There are many potential causes of FUO so it is not possible to list a standard battery of tests which should be performed to investigate every case. It is preferable to tailor the investigations according to clues which may have been suggested by the history and

repeated physical examinations. Table 3 lists clues to the cause of an FUO suggested by information identified from the history.<sup>13</sup>

Repeated, careful and targeted physical examination may reveal physical signs missed on previous examinations. It is worth documenting a careful examination of the sinuses for tenderness, the oropharynx, fundi, skin and nails, thyroid gland, lymph nodes, external genitalia and rectum. All too frequently these are omitted from the physical examination or performed in a cursory way and important signs omitted. This can result in diagnostic delay and wasted resources

performing unnecessary tests. Table 4 indicates clues to the cause of an FUO which may be elicited by physical examination (this list is not exhaustive).

## Treatment

### *Disease-modifying treatment*

In considering treatment of FUO, the concern is essentially with symptomatic treatment because, by definition, the underlying disease is unknown. Specific disease-modifying treatment can usually be commenced only once the diagnosis has been established. The exception is when empirical drug therapy is used to

**Table 4. Clinical findings which may suggest specific diagnoses in patients with fever of unknown origin.** Adapted from Reference 6.

Finding on clinical examination	Suggested diagnosis
Tenderness of facial sinuses or mastoid	Sinusitis
Temporal artery tenderness or nodularity	Temporal arteritis
Tenderness of a tooth	Periapical dental abscess
Choroidal tubercle on fundoscopy	Tuberculosis, sarcoidosis or syphilis
Roth's spots on fundoscopy	Endocarditis
Enlarged tender thyroid and/or bruit	Thyroiditis
Cardiac murmur	Endocarditis
Splenomegaly	Lymphoma, endocarditis, leishmaniasis
Lymphadenopathy	Lymphoma, tuberculosis, HIV
Perirectal tenderness and fluctuance	Perirectal abscess
Prostatic tenderness on rectal examination	Prostatitis or prostate abscess
Testicular nodule on genital examination	Polyarteritis nodosa
Epididymal nodule on genital examination	Tuberculosis, sarcoidosis
Tenderness over calf muscles	Deep vein thrombosis
Petechiae, splinter haemorrhages, subcutaneous nodules or clubbing	Infected pressure sore and/or underlying osteomyelitis
Ulceration over pressure areas or affecting toes	Endocarditis or vasculitis

attempt to confirm or refute a suspected diagnosis. Giving empirical antibiotic therapy for a patient with an FUO is usually not appropriate. If the fever responds without a specific diagnosis being established, there is a risk that an important condition such as endocarditis may be missed. This may result in a potentially adverse outcome in that the endocarditis is suppressed but not cured and the patient subsequently relapses.

Empirical therapy with antituberculosis drugs can be used as a therapeutic trial if extrapulmonary tuberculosis (TB) appears likely, but there is little potential for obtaining a positive mycobacterial culture. However, if rifampicin is included among the empirical anti-TB drugs it must be remembered that this antibiotic could suppress fever in many other conditions including brucellosis and osteomyelitis. Therefore, many clinicians omit rifampicin from therapeutic trials of anti-TB drugs.

### Symptomatic treatment

There are two important issues to take into account when considering symptomatic treatment:

- 1 Will the symptomatic treatment mask the clinical signs and thus hinder diagnosis?
- 2 Could the symptomatic treatment affect the prognosis of any of the potential differential diagnoses?

**Antipyretic agents.** Antipyretic drugs are frequently overprescribed in patients with fevers, particularly among inpatients with recent onset of fever. The masking of temperature by paracetamol and non-steroidal drugs can lead to the erroneous conclusion that a patient is recovering. Therefore, fever in hospitalised patients should usually be treated only if it poses a threat to the patient or is causing substantial discomfort. Treatment of fever is less likely to obscure the diagnosis in patients with an established FUO than in hospital inpatients with recent symptoms. This is both because the established fever is unlikely to subside completely and because the longer duration of symptoms means that apparent short-term resolution of fever should be interpreted with caution.

Historically, the pattern of fever has been said to correlate with specific conditions, but this is rarely diagnostically

useful in the individual patient (except perhaps in malaria). Antipyretic drugs are unlikely to affect the prognosis of conditions causing FUO, so it is not unreasonable to give them to patients with FUO if they are suffering discomfort, particularly if they are being investigated as outpatients.

**Steroids.** If corticosteroids are used as a therapeutic trial, they may mask symptoms (eg rashes and fever). If the patient has an underlying haematological malignancy, steroids may potentially adversely affect future treatment response. Thus, if a therapeutic trial of steroids is being considered for a suspected CTD such as temporal arteritis or polymyalgia rheumatica, the clinician needs to be certain that the patient does not have an occult lymphoma or other malignancy.

### Summary

There are many potential causes of FUO. Most cases are due to unusual presentations of common diseases rather than rare or exotic diseases. The key to establishing the diagnosis is a careful history and careful repeated examinations followed by targeted investigations.

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