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## Fever of Unknown Origin

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### Synonyms

Fever of obscure origin; Fever of unexplained origin; Fever of unknown origin; Pyrexia of unknown origin

### Definition

Fever of unknown origin is a clinical syndrome of fever that does not resolve spontaneously within 3 weeks, and the cause remains unknown after extensive work-up. Fever is defined as an elevation of the body temperature that exceeds the normal daily variation. The hypothalamus controls the body temperature, and a normal body temperature is ordinarily maintained because the hypothalamic thermal regulatory center balances the excess heat production derived from metabolic activities in the muscles and the liver with heat dissipation from the skin and lungs. Normally, healthy adult individuals have a mean oral temperature of  $36.8\text{ }^{\circ}\text{C} \pm 0.4\text{ }^{\circ}\text{C}$ . The temperature is a little bit higher in the evening. Fever of unknown origin is an important clinical challenge. In 1961 Petersdorf and Beeson (1961)

defined it in their first report as an illness characterized by fever of more than 3 weeks' duration, with temperatures of more than  $38.3\text{ }^{\circ}\text{C}$  and failure to identify the origin of the fever despite 1 week of hospitalization. Because of the development of diagnostic procedures, increasing costs of hospital care, and the increasingly outpatient work-up, the definition was modified in 2003, and a hospital setting was no longer needed for assessment of the illness.

### Characteristics

Over the last decades, several case series have examined the underlying diseases for fever of unknown origin. More than 200 causes have been reported to cause fever of unknown origin.

After work-up, fever of unknown origin has generally been considered to be caused by infections, neoplasms, and an inflammatory or a heterogeneous group of other diseases. The most common infections reported in the literature are tuberculosis and intra-abdominal abscesses. Other important causes are temporal arthritis and other collagen vascular diseases and venous thromboembolism. One is unable to establish the causal diagnosis in 9–25 % of the cases.

In the early case series, the proportion of cancers varied between 7 % and 24 %. Although most causes of fever of unknown origin resolve spontaneously, the risk of occult cancer remains a concern. It is important to emphasize that most

studies on the origin of fever of unknown origin did not include any control groups or a reference standard and criteria and the final diagnosis was defined in many different ways.

### Cancer and Fever of Unknown Origin

Although several studies have been conducted on the association between fever of unknown origin and a subsequent diagnosis of cancer, the studies have been small; based on 40–300 patients, several studies have been based on referral centers and almost all studies lack control groups.

Nearly all common cancers in the literature had a link to fever of unknown origin. In the referral center, case series of a proportion of cancer diagnosed in patients with fever of unknown origin has decreased from about 30 % of cases in the 1970s to 9–20 % in the 1990s. It has been suggested that improved diagnostic imaging with, e.g., CT and MRI has improved the detection of otherwise occult solid tumors.

In 2005 a large, Danish population-based study based on health care databases assessed the risk of cancer in 43,205 patients hospitalized from 1977 to 1997 with fever of unknown origin. Data on patients with a discharge diagnosis of fever of unknown origin were linked to the Danish Cancer Registry. The incidence rate of cancer was compared with the expected cancer incidence rate in the general population. The median follow-up was 6.3 years: 9,932 of the patients were more than 60 years old, and 399 cancer cases were diagnosed during the first year of follow-up among the 43,205 patients with a relative risk (standardized incidence rate ratio) of 2.3 (95 % CI 2.1–2.5). The relative risk was raised for various types of cancer, especially for ► [Hodgkin disease](#) (relative risk 27.8, 95 % CI 15.9–45.1), non-Hodgkin ► [lymphoma](#) (relative risk 9.9, 95 % CI 7.1–13.3), ► [leukemia](#) (relative risk 5.6, 95 % CI 3.9–7.8), and ► [multiple myeloma](#) (relative risk 4.4, 95 % CI 2.1–8.0), as well as sarcoma (relative risk 6.6, 95 % CI 3.6–11.1) and solid tumors in the liver (relative risk 6.1, 95 % CI 3.2–10.7), gall bladder (relative risk 2.7, 95 % CI 0.9–6.3), brain (relative risk 4.1, 95 % CI 3.5–6.2), kidney (relative risk 2.6, 95 % CI 2.6; 95 % CI 1.4–4.5), colon (relative risk 2.7, 95 %

CI 2.0–3.5), and pancreas (relative risk 3.7, 95 % CI 2.3–5.6).

During 1–19 years for hospitalization for fever of unknown origin, 1,097 cancer cases were observed compared with 977.8 cancer cases expected. During the follow-up period, there was still an increased relative risk of hematological cancer as Hodgkin disease (relative risk 2.1, 95 % CI 1.1–3.8), non-Hodgkin lymphoma (relative risk 1.4, 95 % CI 1.0–1.9), leukemia (relative risk 1.7, 95 % CI 1.3–2.2) and multiple myeloma (relative risk 1.6, 95 % CI 1.0–2.4), liver (relative risk 1.9, 95 % CI 1.1–2.9), brain (relative risk 1.4, 95 % CI 1.0–1.9), and kidney cancer (relative risk 1.5, 95 % CI 1.1–2.1). Until publication of the Danish study, the former studies on cancer risk had included a total of 1,200 fever of unknown origin patients. The absolute risks of cancer during the first year of follow-up were low, much lower than those reported in former studies.

### Diagnosis

There are no randomized clinical trials in the literature about the clinical utility of different diagnostic strategies. Mourad et al. (2003) have suggested the following minimal to qualify as fever of unknown origin: comprehensive history, physical examination, complete and differential blood cell count, blood film reviewed by hematopathologist, routine blood chemistry, urinalysis and microscopy, blood and urine cultures, antinuclear antibodies, rheumatoid factor, human immunodeficiency virus antibody, cytomegalovirus IgM antibodies, heterophile antibody test, Q fever serology, chest radiography, and hepatitis serology. To obtain a cancer diagnosis, abdominal CT scan is the most central diagnostic test, but further diagnostic work-up depends on symptoms and findings.

### Prognosis of Cancer Associated with Fever of Unknown Origin

The underlying disease is the main predictor for the outcome of fever of unknown origin. Four studies have shown that 52–100 % of patients with fever of unknown origin and cancer will die within 5 years after the diagnosis. In the

Danish database study of the 399 cases of cancer, the extent of cancer was compared for cases associated with fever of unknown origin and 3,958 similar cancer cases that did not have fever of unknown origin. Cancer diagnosed in patients with fever of unknown origin during the first year of follow-up was associated with higher prevalence of metastases and an increased mortality ratio of 1.4. After 1 year of follow-up, the cumulative survival among cancer cases was about 50 % and after 2 years about 35 %.

A diagnosis of cancer subsequent to hospitalization because of fever of unknown origin does not necessarily imply an extremely poor prognosis.

### Conclusion

The existing literature has consistently shown that fever of unknown origin is a marker of occult cancer. The last Danish study showed that this association in a population-based setting is weaker than reported in former studies, but the relative risk remains increased many years subsequent to the hospitalization for fever of

unknown origin for hematological, liver, brain, and kidney cancer. Fever of unknown origin is associated with more advanced cancer disease and a poor prognosis compared with similar cancer patients without fever of unknown origin, but the prognosis is not extremely poor.

### References

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