



## Fever of unknown origin in cancer patients



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### Contents

1. Introduction .....	125
1.1. Historical perspectives .....	125
1.2. New concepts .....	126
2. FUO in cancer patients .....	126
2.1. Review of the literature .....	126
2.2. Pyrogenic cancers: the concept .....	126
2.3. Pyrogenic cancers: case reports .....	127
2.4. Limitations of the study .....	127
3. Management of FUO in neutropenic patients .....	127
3.1. Importance of FUO during neutropenia .....	127
3.2. Empirical therapy for FUO .....	128
4. Prevention of fever in neutropenic cancer patients .....	128
4.1. Chemoprophylaxis .....	128
4.2. Prevention of fungal infections .....	128
4.3. Use of G-CSF for prophylaxis of infection .....	128
5. Diagnostic procedures .....	129
5.1. Role of FDG PET/CT in evaluation of FUO .....	129
5.2. Other diagnostic approaches .....	129
6. Conclusions .....	129
Conflict of interest .....	129
Funding .....	129
Acknowledgement .....	129
References .....	129

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### ABSTRACT

Fever of unknown origin (FUO) remains a challenging clinical problem, namely in patients with cancer. In cancer patients, FUO may be due to the cancer itself, as it is the case of hematological malignancies; digestive tumors (colon cancer, liver metastases) are significantly associated with FUO and infection can be demonstrated in some cases. Prevention with G-CSF and empirical antimicrobial therapy are essential approaches for the management of FUO in cancer patients. New diagnostic approaches, such as PET imaging, should be further evaluated in cancer patients with FUO.

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## 1. Introduction

### 1.1. Historical perspectives

Fever of unknown origin has been a challenging problem for internists for several decades, since the Petersdorf and Beeson's classical article classifying the causes of fever of unknown origin

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(FUO). Classic FUO, as they define it, is a temperature rise over 38.3 °C (101 °F) on several occasions over a period of more than 3 weeks, for which no diagnosis has been reached despite one week of inpatient investigation (Petersdorf and Beeson, 1961).

This seminal observation has been made at a time when the diagnostic possibilities, namely biological and radiological, were relatively limited. According to Petersdorf and Beeson, FUOs were due to infection in 36% of the patients, to malignancy in 19% and to collagen-vascular diseases in 19%; no cause of fever could be detected in 7% of the patients. Paradoxically in spite of a tremendous development of our diagnostic capabilities, the rate of undiagnosed FUO has progressively increased over the years to a greater than 50% incidence (Horowitz, 2013), leading to a new concept of “fever of too many origins” seen presently in hospitalized patients with many morbidities, having received sophisticated investigations and numerous specific and less specific treatments.

In 1973, Klustersky et al. explored the etiology of FUO in patients with cancer and showed that infection was responsible for the fever in 57% of the patients and the neoplasia itself was responsible for it in 38% (Klustersky et al., 1973).

In 1990, Durack and Street have anticipated the coming complexity of FUO in modern medicine and have proposed to divide FUOs into four groups: classical, nosocomial, neutropenic and HIV-associated (Durack and Street, 1991).

The recently published studies, confirm the drastic change in the diagnostic spectrum of FUO. Vanderschueren et al., have confirmed that, despite the technological progresses of the last years in terms of diagnosis skills, the origin of fever remains elusive in many patients. In their study, the cause of fever remained undiagnosed in 48%; among the patients with a final diagnosis, non-infectious inflammatory diseases were the most common cause of FUO (35%) surpassing infection (30%) and malignancies (15%) (Vanderschueren et al., 2003). Based on these observations, they introduced the concept of “inflammation of unknown origin” (IUO) and suggested that the 38.3 °C limit may be arbitrary and that the diagnostic procedures used in FUO can be applied in IUO (Vanderschueren et al., 2009).

In another recent study by Bleeker-Rovers et al., 2007 it was shown that infection was the cause of FUO in 16% of the patients, neoplasia in 7% and non-infectious inflammatory diseases in 22%; in 51% the cause of fever was not found. In both studies (Vanderschueren et al., 2009; Bleeker-Rovers et al., 2007) the mortality rates in patients with undiagnosed FUO was very low (Table 1).

## 1.2. New concepts

As a conclusion to this introductory section, we may state that the classical concept of FUO is being replaced by a syndrome consisting of an inflammatory state (IUO), with or without fever, which etiology is most often multifactorial. The diagnostic approaches of that syndrome, in order to define more precisely the etiologies responsible for it, and consequently, better orient therapy, remain to be investigated.

Nonetheless, still some patients will present the classic FUO and the Durack and Street classification of FUO into four groups, definitely helps to better select possible diagnoses and orient more specifically the treatment (Durack and Street, 1991). Recently, FUO in older patients has been reviewed by Hayakawa et al., 2012; fever may be blunted or absent in a substantial proportion of infected geriatric patients and, at the same time, fever is likely to be associated with a serious infection compared to younger febrile patients. FUO or IUO in pediatric patients probably also deserve a special focus.

Finally, it should be recognized that FUO or IUO have demographic (geographical) specificities and that data obtained from

**Table 1**  
Changes in the causes for FUO over the last 50 years.

Studies	Infection	Cancer	Collagen or inflammatory disease	Unknown origin
Petersdorf and Beeson (1961)	36%	19%	19%	7%
Vanderschueren et al. (2003)	30%	15%	35%	48%
Bleeker-Rovers et al. (2007)	16%	7%	22%	51%

studies in some countries are not necessarily applicable to patients in other countries with different epidemiology and medical systems: e.g., infection, especially tuberculosis, was the leading etiology of FUO in several recent reports from Asia (India, China, Pakistan) (Shi et al., 2013).

## 2. FUO in cancer patients

### 2.1. Review of the literature

In 1961, Browder et al. (Browder et al., 1961) studied the significance of fever in patients with neoplastic diseases in 343 patients with cancer admitted to a general hospital over a 1-year period. They found a high incidence of fever in those patients with cancer and their data strongly suggested that infection or localized obstruction produced by the tumor was responsible for the fever, which, in most instances, disappeared spontaneously. They also stated that fever due to cancer was rare: in about 5% of their patients.

More recently, Toussaint et al., 2006 conducted a similar study in 477 cancer patients admitted with fever to a cancer hospital. Infection, non-infectious causes (drugs, metastases, primary tumor, post-surgery) and FUO were responsible for the fever in 67, 23 and 10% respectively. Non-infectious causes were due to the neoplasia itself, and were the most frequent cause (41%) in non-neutropenic patients; in neutropenic patients, 13% of fevers were due to non-infectious causes, mainly medications.

As already mentioned, Klustersky et al., 1973 explored the causes for FUO, defined following original Petersdorf and Beeson's criteria (Petersdorf and Beeson, 1961), in 100 patients with cancer. Infection caused the fever in 37% of the patients; fever could be attributed to the neoplasia itself in 18 patients (38%): 5 had acute leukemia in relapse, 6 had extensive lymphomas, 7 presented with widespread metastatic carcinomas and, in 6 of them, large liver metastases were present. Overall, FUO was a relatively rare event in that population (0.7%).

In the study by Vanderschueren et al., 2003, FUO caused by the neoplasia was seen in 15% of 192 patients; most had Hodgkin's disease, lymphomas, leukemia or angioimmunoblastic lymphadenopathy; solid tumors were found only in 7 patients.

In the study of Bleeker-Rovers et al., 2007, neoplasia was responsible for 7% of 73 patients with FUO; 3/5 patients had lymphomas.

### 2.2. Pyrogenic cancers: the concept

Thus, as summarized in Table 2, FUO in non-neutropenic cancer patients is not due generally to neoplastic disease as shown in several studies conducted during the last decade; a credible figure is 10% and many such patients have hematological malignancies, namely lymphomas. Other malignancies presenting more than occasionally as FUO's are colon cancer and large hepatic metastases or hepatocarcinomas. It should be stressed that many different tumors have been reported as having an initial presentation as FUO.

“Pyrogenic cancers” were often considered to be in patients with lymphoma, leukemia, immunoblastic lymphadenopathy, lymphomatoid granulomatosis, malignant histiocytosis, colon cancer,

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