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**Original Article**

## Fever of unknown origin: Revisit of 142 cases in a tertiary Chinese hospital

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**Summary** To investigate the causes of fever of unknown origin (FUO), we analyzed the clinical data on 142 patients with FUO admitted to our department from January 2002 to December 2003. After various examinations and specific treatment, a definitive diagnosis was reached in 122 cases. Of them, 51 cases (35.9%) were caused by infections, 46 (32.4%) were due to autoimmune diseases, 18 (12.7%) were due to tumors, 7 (4.9%) were due to other diseases, and in 20 (14.1%) the cause was still unknown after hospitalization. In conclusion, infection is the main cause of FUO. Autoimmune diseases and malignant tumors are both significant causes. Most patients with an FUO were ultimately diagnosed with various examinations and careful analysis.

**Keywords:** Fever of unknown origin, Retrospective studies

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### Introduction

Fever of unknown origin (FUO) is extremely difficult to diagnose. It has been defined as an illness with a rectal temperature exceeding 38.3°C on at least three occasions, lasting at least 3 weeks, and with no diagnosis reached after 1 week of inpatient investigation (1). Many prospective studies of patients with FUO have been performed around the world using this definition. In 1991, Durack and Street (2) proposed that the requirement of one week of inpatient investigation be modified to either days of inpatient investigation or three visits without discovering the source of fever. China has followed the original criterion of Petersdorf RG because of economic factors. The spectrum of diseases seems to be determined by geographic and economic factors, and it appears to change with time (3).

### Materials and Methods

A total of 142 patients seen by this department from January 2002 to December 2003 were included in a 2-year study. The inclusion criteria were: (a) fever

for at least 3 weeks; (b) fever > 38.3°C at least twice; (c) absence of diagnostic suggestions (diagnostic hypotheses) after history, clinical examination, and a series of screening investigations. Patients with immune deficiency were excluded.

### Results

During the two-year period of the study, 142 patients were followed up as FUO. Of the 142 patients, 69 were male and 73 were female. The mean age was 48.7 years, with ages ranging from 14 to 81. Twenty-five patients (17.6%) were older than 65. A diagnosis was reached for 122 (85.9%) patients. No diagnosis was reached for twenty patients (14.1%), three of whom recovered spontaneously. Of those, 14 deteriorated rapidly; these patients were presumed to have had a malignant disease upon discharge and died without necropsy because of customs prohibiting it. Infections were found in 51 (35.9%) patients, autoimmune diseases in 46 (32.4%), neoplasm in 18 (12.7%), and miscellaneous diseases in 7 (4.9%).

Infections were observed to be the most common aetiology of FUO (Table 1). Infectious causes of FUO are shown in Table 2. The mean age of affected patients was 51.7 years of age. Patients broke down into 26 males with a mean age of 49.8 years and 25 females with a mean age of 53.8 years. Salmonellosis was diagnosed in 8 patients who had atypical and mild

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**Table 1.** The diagnostic categories of 142 cases

Diagnostic category	No of patients (n = 142)	%
Infection	51	35.9
Autoimmune disease	46	32.4
Neoplasm	18	12.7
Miscellaneous	7	4.9
No diagnosis	20	14.9

**Table 2.** Infectious causes

Diagnostic category	No of patients (n = 51)
Bacterial infection	36
Salmonellosis	7
Infective endocarditis	7
Tuberculosis	6
Pulmonary tuberculosis	4
Tuberculous peritonitis	1
Intestinal tuberculosis	1
Urinary tract infection	5
Blood stream infection	4
Pneumonia	4
Biliary tract infection	1
Liver abscess	1
Odontogenic fever	1
Viral infection	5
Fungal infection	3
Mycoplasma pneumonia	5
Malaria	2

**Table 3.** Autoimmune disease

Diagnostic category	No of patients (n = 46)
UCTD	10
Adult Still's disease	8
SLE	8
Dermatomyositis	3
Ankylosing spondylitis	3
Multiple myositis	2
Polymyalgia rheumatica	2
Mixed connective-tissue disease	2
Rheumatoid arthritis	2
Urticarial vasculitis	1
Scleroderma	1
Behcet's disease	1
Autoimmune liver disease	1
Overlap syndrome	2

**Table 4.** Neoplastic causes

Diagnostic category	No of patients (n = 18)
Lymphoma	8
Myelodysplastic syndrome	2
Cancer of unknown primary site	2
Gastrointestinal tract Ca	2
Malignant histiocytosis	1
Hemophagocytic syndrome	1
Langerhans cell histiocytosis	1
Thyroid adenoma	1

**Table 5.** Miscellaneous diseases

Diagnostic category	No of patients (n = 7)
Drug fever	2
Necrotic lymphadenitis	2
Digestive tract ulcer	1
Post-infection status	1
Chronic fatigue syndrome	1

symptoms. Infective endocarditis was determined to be the cause of fever in seven patients. Urinary tract infection was diagnosed in 5 patients. Chronic

pyelonephritis with obstruction of the ureter was diagnosed in 2 patients by abdominal CT. Chronic recurrent prostatitis was found in two male patients. Atypical pneumonia was found in 4 patients who were elderly or had already received extensive antimicrobials.

Table 3 shows autoimmune causes. The mean age of affected patients was 45.5 years of age, with ages ranging from 14 to 80. Patients broke down into 16 males with a mean age of 49.9 years and 32 females with a mean age of 43.4 years. There were more female than male patients, and the mean age was lower for females than males but the difference was not statistically significant. The most significant autoimmune causes were UCTD (undifferentiated connective tissue disease), SLE, and adult Still's disease.

Table 4 shows neoplastic causes. The mean age of affected patients was 53.7 years of age, with ages ranging from 19 to 71. Patients broke down into 12 males with a mean age of 54.3 years and 6 females with a mean age of 52.5 years. Lymphoma was the most significant cause. All 8 lymphoma cases were diagnosed by clinical and pathological evidence, *i.e.* bone marrow biopsy in 2 patients and lymph node biopsy in 6 patients. There were more male than female patients; the mean age differed but the difference was not statistically significant.

Details on miscellaneous diseases not falling under the preceding categories are shown in Table 5.

## Discussion

In this study a diagnosis could not be reached for 14.1% of the cases. There may be no definitive diagnosis (9-25.6%) in some cases (1,2,4-6). In the current study, the causes of FUO were infections (35.9%), autoimmune diseases (32.4%), neoplasms (12.7%), and miscellaneous diseases (4.9%). Infections were still the most frequent cause of FUO but their frequency was lower than that reported in other studies (1,2,4-6). There were many factors contributing to these causes. One factor may be the ease with which patients receive extensive antimicrobial therapy. In this study, autoimmune diseases were the second most significant cause of FUO and were more frequent than in other studies (7). Many doctors who work in non-teaching hospitals had limited awareness of autoimmune diseases, so patients were limited to teaching hospitals.

Neoplasms were the third most significant cause of FUO in this study. The use of CT and MRI imaging allows tumors to be more easily detected (3). However, diagnosing hematological malignancies can still be difficult because of the absence of localized symptoms. Perhaps this explains why lymphoma and myelodysplastic syndromes were frequently identified in patients with FUO. Diagnosis of atypical lymphoma is difficult; multiple lymphonode biopsies may help

in diagnosis. Cancer of unknown primary site (CUPS) (8) was also a significant cause of neoplasms. In these cases, cancer cells were found in pleural or peritoneal effusions but the primary tumor was not found.

There were more undiagnosed cases at discharge than in other studies (6). Only three of those patients recovered spontaneously. Fourteen who deteriorated rapidly were presumed to have had a malignant disease upon discharge; they died but a necroscopy was not performed because of local customs and economic factors. In other studies, most cases of FUO led to a diagnosis and in undiagnosed cases all or most of the patients recovered spontaneously (4,7,9).

Causes of FUO and their relative frequencies in the population should be known because FUO is usually caused by either an uncommon condition or an unusual presentation of a well-known disease. Thus, frequent diseases rather than rare ones should be considered first when diagnosing FUO.

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