A Retrospective Review of 226 Hospitalized Patients with Fever

Masashi Goto¹, Hiroshi Koyama², Osamu Takahashi² and Tsuguya Fukui³

Abstract

Objective To describe characteristics and outcomes for patients hospitalized with fever, not only patients with fever of unknown origin (FUO).

Methods Medical records were reviewed for 226 consecutive patients hospitalized in a Japanese referral hospital with fever as one of the clinical problems.

Results Although the majority of illnesses involved some sort of infection (54%), noninfectious inflammatory diseases, particularly adult Still's disease (n=6) and primary vasculitis syndromes (n=5) including 3 cases of Behçet's disease, represented the leading cause in patients who met the definition of FUO [16/51 (31%)]. Tuberculosis (n=6) and psychological disorders (n=6) were associated with late diagnosis. However, there was only one patient meeting the definition of FUO among those with a psychological disorder. Among the patients with prolonged fever who did not strictly meet the definition of FUO, there was a considerable number of patients with critical illnesses, such as intra-abdominal abscess, polymyalgia rheumatica, sarcoidosis, ulcerative colitis, Castleman's disease, hematological and solid malignancies, and panhypopituitarism. Drug-induced fever, systemic viral infection and unspecified vasculitis were difficult to definitively diagnose, although these pathologies were suspected as causes of fever. Follow-up of patients without definitive diagnosis at discharge confirmed that the fever subsided spontaneously or the cause of fever was properly treated after diagnosis in every patient and that none died of the underlying febrile illness.

Conclusions The present findings, from all patients displaying fever at hospitalization, are in agreement with findings from prior FUO series. Strict use of the definition of FUO is thus unwarranted when managing patients with prolonged fever.

Key words: fever, fever of unknown origin, retrospective chart review, diagnosis, prognosis

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Introduction

Numerous patients present with fever at admission. Fever may be a symptom of an underlying serious condition, and is sometimes the only diagnostic clue. Fever of unknown origin (FUO), a clinical syndrome that may result from many common etiologies, is characterized by a prolonged fever without other signs or symptoms indicative of a well-defined process. Since reports of FUO first appeared in the literature about 70 years ago (1), the diagnosis of FUO has continued to represent a clinical challenge. Recent advances in imaging techniques and the emergence of drug-resistant

bacteria and new viral infections have changed the profile of FUO (2, 3).

Recently, use of the term FUO has been criticized as imprecise and arbitrary at best, and the evaluation methods applied to patients to reach such a diagnosis are said to lack uniformity (4). Nevertheless, few studies have investigated the characteristics of hospitalized patients with fever, including patients meeting FUO criteria and patients who do not. The present study was conducted to determine the characteristics and outcomes for patients hospitalized with fever in a general internal medicine ward in a Japanese tertiary referral hospital. In addition, we examined whether patients with FUO differ substantially from patients with fever, not only

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¹ Kyoto University Health Service, Kyoto, ² Department of General Medicine and Clinical Epidemiology, Kyoto University Graduate School of Medicine, Kyoto and ³ St. Luke's Life Science Institute & St. Luke's International Hospital, Tokyo

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Correspondence to Dr. Masashi Goto, goto@msa.biglobe.ne.jp

patients with FUO, in order to gain some insight into the management of patients with prolonged fever.

Methods

Medical records were retrospectively reviewed for all hospitalization episodes in the Department of General Medicine in Kyoto University Hospital between January 1, 1994 and December 31, 2002. Patients were included if: 1) fever was listed among the chief complaints; or 2) high body temperature was documented from physical examination on admission. An axillary temperature $\geq 37.0^{\circ}\text{C}$ was considered a high body temperature. Patients with a chief complaint of fever but whose body temperature had normalized on admission and for whom fever was not documented during hospitalization were excluded. Patients admitted due to other conditions who developed fever after admission were likewise excluded from this study. Patients hospitalized twice or more during the study period were counted as separate hospitalization episodes if a cause of fever had been determined and properly treated in each hospitalization. On the other hand, a series of hospitalizations were counted as one if the patient was rehospitalized due to recurrence of fever whose cause had not been determined in the prior hospitalizations.

Initially, 3 investigators (M.G., H.K. and O.T.) independently reviewed discharge summaries of all hospitalization episodes. Patients meeting the inclusion criteria were selected and their complete hospital medical records were reviewed to finally determine inclusion and extract the relevant information based on a pre-defined format. When we were not sure that the patient met the inclusion criteria from information in the discharge summary, we were willing to refer to the complete hospital medical records to obtain further information. Because we wanted to enroll all admitted patients fulfilling our criteria, without any unintended selection bias, the complete hospital medical records were reviewed when one of the 3 investigators considered this as necessary to obtain further information. Each hospital medical record was independently reviewed by 2 of the 3 investigators listed above. Disagreements were resolved by re-review and discussion with other investigators.

Hospital medical records were used to determine: definitive cause of fever; number of hospital days until definitive diagnosis; number of days between onset of fever and the first visit to our outpatient department; number of days between first visit and admission; whether the patient had already undergone extensive investigation before referral to our department; maximum body temperature documented in hospital or in the outpatient department; and baseline coexisting conditions. Cause of fever was considered definitive when the likelihood of the diagnosis causing the fever was estimated as $>75\%$ by investigators. Information was also gathered about findings from physical examinations and laboratory tests on admission, such as blood pressure, body temperature, heart rate, respiratory rate, white blood cell (WBC) count, neutrophil count, C-reactive protein (CRP)

level and erythrocyte sedimentation rate (ESR).

If patients did not receive a definitive diagnosis during hospitalization or we were somewhat skeptical about the diagnosis established by the clinicians-in-charge, clinical course after discharge was followed-up using a review of outpatient medical records and/or telephone interviews.

Verbal informed consent was obtained from all participants who received follow-up telephone interviews. As the present study was merely observational and did not require any deviations from standard care, no written informed consent was sought from participants.

Subjects were divided into following 5 categories based on cause of fever, as often used in previous studies on FUO: infections; noninfectious inflammatory diseases (NIID); neoplasms; miscellaneous causes; and no diagnosis. Descriptive terms such as “granulomatous hepatitis” and “nonspecific myositis” were not considered final diagnoses and were reclassified into the “no diagnosis” category. Demographic characteristics and number of days between onset and first visit and between first visit and admission were compared across these 5 categories by the use of Kruskal-Wallis test for continuous or interval variables and Fisher’s exact test for a categorical variable. Demographic characteristics, number of days between onset and first visit and between first visit and admission, findings on physical examination and laboratory data were then compared between patients who met the definition of FUO and patients not meeting FUO criteria for whom the cause of fever was not determined within 3 days of investigation and between patients who died during hospitalization and patients who did not. The Wilcoxon rank-sum test was used to compare continuous and interval variables, while Fisher’s exact test was used for a categorical variable. FUO was defined as 1) an axillary temperature of $>38.0^{\circ}\text{C}$, which was thought to correspond to an oral temperature of $>38.3^{\circ}\text{C}$; 2) a duration of fever of >3 weeks; and 3) failure to reach a diagnosis despite 3 outpatient visits or 3 days of inpatient investigation (5).

Analyses were computed using STATA 9.1 software (STATA Corporation, College Station, Texas, 2006). All tests of significance were two-tailed and values of $P<0.05$ were considered statistically significant.

Results

There were a total of 664 hospitalization episodes in the Department of General Medicine in Kyoto University Hospital during the study period. From these, 276 candidate episodes were selected from the discharge summaries of the hospital medical records. After excluding 50 hospitalization episodes by reviewing the complete hospital records, 226 hospitalization episodes were included in the present analyses. There were 8 patients hospitalized with fever twice during the study period. For 2 of these 8 patients, we counted the 2 hospitalizations as one because they were rehospitalized due to recurrence of fever whose cause had not been determined in the first hospitalization. There were no human

Table 1. Demographic Characteristics of subjects for Each Disease Category*

	All patients	Infections	NIID	Neoplasms	Miscellaneous	No diagnosis	P-value
N (% of total)	226 (100)	122 (54.0)	29 (12.8)	16 (7.1)	33 (14.6)	26 (11.5)	—
Age, y	50 (26-67)	51.5 (27-69)	48 (24-57)	57.5 (43.5-76)	37 (24-57)	52.5 (25-65)	0.17
Sex							
Men	111 (49.1)	63 (51.6)	11 (37.9)	6 (37.5)	17 (51.5)	14 (53.9)	0.58
Women	115 (50.9)	59 (48.4)	18 (62.1)	10 (62.5)	16 (48.5)	12 (46.1)	
Patients with underlying conditions	122 (54.0)	70 (57.4)	11 (37.9)	8 (50.0)	19 (57.6)	14 (53.9)	0.43
Max. body temperature [†] , °C	38.2 (37.4-38.9)	38.2 (37.5-38.9)	38.7 (37.7-39.1)	38.5 (37.9-39.3)	37.7 (37.4-38.3)	38.3 (37.2-39.0)	0.07
Interval from onset to first visit [‡] , d	12 (4-35)	7 (3-19)	30 (14-173)	49.5 (30-116)	15 (3-95)	17.5 (5-39)	<0.001
Interval from first visit to admission [§] , d	2 (1-6)	1 (1-3)	4 (3-11)	2.5 (1-12.5)	1 (1-4)	7 (2-14)	<0.001
Referral after extensive investigations	39 (17.3)	11 (9.0)	12 (41.4)	3 (18.8)	6 (18.2)	7 (26.9)	0.001
FUO [¶] (% of FUO total)	51 (100)	13 (25.5)	16 (31.4)	8 (15.7)	3 (5.9)	11 (21.6)	—

Abbreviations: NIID, noninfectious inflammatory diseases; FUO, fever of unknown origin.

* Data are number (percentage) or median (interquartile range) unless otherwise specified.

† Maximum body temperature documented in hospital or in the outpatient department.

‡ Number of days between onset of fever and first visit to our outpatient department.

§ Number of days between first visit and admission.

|| Patients referred to our department without definitive diagnosis in spite of extensive investigation.

¶ Number of patients meeting the definition of FUO.

Figure 1. Timing of diagnosis and proportion of disease categories. Abbreviation: NIID, noninfectious inflammatory diseases.

immunodeficiency virus positive patients or neutropenic patients. Overall, there were discrepancies between 2 of the 3 investigators in 597 (17.6%) of 3,390 extracted items, ranging from 1.6% to 35.5% depending on the type of item extracted. All discrepancies were resolved by consensus.

Demographic characteristics by disease category

Table 1 shows the demographic distribution of patients among disease categories. The neoplasm category showed older patients, the miscellaneous cause category showed younger patients and lower body temperature, and the NIID category showed fewer patients with underlying conditions, even though there was no statistical significance. The interval between onset of fever and first visit was longer in patients with neoplasms or NIID than in patients with infections. However, neoplasms did not require as many days from first visit to admission as from onset to first visit. Instead, the undiagnosed patients displayed a longer duration from first visit to admission. Thirty-nine patients (17.3%) were referred to our department from other medical institutions without a definitive diagnosis in spite of extensive investigation. Patients with NIID were more likely to be referred because of the difficulty of diagnosis. FUO criteria were fulfilled by 51 patients (22.6%).

Timing of definitive diagnosis

Fig. 1 indicates the proportion of each disease category according to the duration before cause of fever was determined. There was only one patient diagnosed in the outpatient department after 3 visits. She was diagnosed as aspiration pneumonia on her 4th visit. Most of the illnesses diagnosed on the first visit were infections (84.6%). The proportion of infections gradually decreased over time, while the proportion of NIID gradually increased. Nearly half of the patients with infections (45.9%) were diagnosed before admission. Meanwhile, cause of fever was determined after admission for most patients in other disease categories (87.2%).

Diagnoses in each disease category

Table 2 separately lists definitive diagnoses for each disease category according to whether the diagnosis was reached within 3 days of investigation and whether the definition of FUO was fulfilled. Among infections diagnosed within 3 days, acute respiratory and urinary tract infections were the leading causes of hospitalization. The 2 patients who were eventually diagnosed as extrapulmonary tuberculosis (tuberculous meningitis and lymphadenitis) both met the definition of FUO. Chronic pyelonephritis sometimes took a long period to determine as the cause of fever. None of the 3 patients with infective endocarditis, which used to be a frequent etiology of FUO, required >3 days for definitive diagnosis, although one required 122 days from onset of fever to first visit to our outpatient department. Patients with NIID were more likely to meet the definition of FUO. Adult Still's disease and primary vasculitis syndromes including 3 cases of Behçet's disease and 1 case of microscopic polyangiitis were the most prevalent conditions among FUO patients. All 4 cases with hematological malignancies were not diagnosed within 3 days. The proportion of patients meeting the definition of FUO among those diagnosed after day 3 was lower in the miscellaneous cause category than in other disease categories. All patients whose fever was caused by psychological problems, including somatoform disorder, psychogenic fever, irritable bowel syndrome, and factitious disorder, required more than 3 days until definitive diagnosis

Table 2. Diagnoses in each Category Separated According to Whether Diagnosis was Made Within 3 Days of Investigation and Whether the Definition of FUO was Fulfilled.

	Infections	NIID	Neoplasms	Miscellaneous causes
Diagnosed within 3 days of investigation	Central nervous system	Rheumatoid arthritis	Breast cancer	Ureteral calculus
	Viral meningitis	Adult Still's disease	Lung cancer	Cerebral infarction
	Respiratory organs	Microscopic polyangiitis	Small intestinal tumor	Hemorrhagic stroke
	Pneumonia and/or Bronchitis	Takayasu's arteritis	Colon cancer (metastatic)	Varicose syndrome
	Tuberculous pleurisy	Chronic urticaria		Congestive heart failure
	Pulmonary tuberculosis	Idiopathic erythema nodosum		Acute hepatitis (unknown etiology)
	Pharyngitis or Tonsillitis			Gastric ulcer (bleeding)
	Sinusitis			Obstruction of small intestine
	Heart			Thrombocytopenic purpura (drug-induced)
	Infective endocarditis			Non-traumatic rhabdomyolysis
	Abdominal organs			Dehydration
	Acute colitis			Drug-induced fever (carbamazepine)
	Cholecystitis and/or Cholangitis			Drug intoxication due to suicide attempt
	Appendicitis			Exaggerated circadian temperature rhythm
	Intra-abdominal abscess			
	Abdominal wall abscess (urachus)			
	Acute viral hepatitis (type E)			
	Spontaneous bacterial peritonitis			
	Urogenital organs			
	Pyelonephritis			
	Pelvic inflammatory disease			
	Skin			
	Cellulitis			
	Diabetic foot			
	Viral infection			
	Infectious mononucleosis (EBV)			
	Viral-associated hemophagocytic syndrome (EBV)			
	Other viral infections			
	Others			
	Endophthalmitis and Arthritis purulenta			
	Periodontitis			
	Rickettsiosis			
Diagnosed after day 3 The definition of FUO is not fulfilled	Central nervous system	Polymyalgia rheumatica	Hodgkin's disease	Subacute thyroiditis
	Viral meningitis	Sarcoidosis	Castleman's disease	Alcohol withdrawal
	Respiratory organs	Vasculitis (unspecified)	Gastric cancer	Somatiform disorder
	Aspiration pneumonia	Ulcerative colitis	Ovarian cancer	Psychogenic fever
	Bacterial pleuritis (empyema)	Reactive arthritis		Acute deterioration of chronic pancreatitis
	Pharyngitis or Tonsillitis			Irritable bowel syndrome
	Tuberculous pleurisy			Hyponatremia due to primary polydipsia
	Abdominal organs			Patella fracture
	Intra-abdominal abscess			Deep vein thrombosis
	Acute colitis			Dehydration
	Acute appendicitis			Panhypopituitarism due to a brain tumor
	Cholecystitis			
	Urogenital organs			
	Pyelonephritis			
FUO	Skin			
	Keloid-associated skin infection			
	Viral infection			
	Systemic viral infection			
	Infectious mononucleosis (EBV, CMV)			
	Central nervous system	Adult Still's disease	Hodgkin's disease	Recurrent fever associated with progesterone action
	Subdural abscess	Behçet's disease	Malignant lymphoma	Drug-induced fever (penicillin)
	Tuberculous meningitis	Vasculitis (unspecified)	Renal cancer	Factitious fever
	Respiratory organs	Microscopic polyangiitis	Esophageal cancer	
	Tuberculous pleurisy	Rheumatoid arthritis	Rectal cancer	
	Pulmonary tuberculosis	Systemic lupus erythematosus and Sjögren's syndrome	Cholangiocarcinoma	
	Mycobacterium avium complex infection	Crohn's disease	Mycosis fungoides	
	Recurrent aspiration pneumonia	Ulcerative colitis		
	Urogenital organs	Sweet's syndrome		

Abbreviations: NIID, noninfectious inflammatory diseases; FUO, fever of unknown origin; EBV, Epstein-Barr virus; CMV, cytomegalovirus.

(n=6), but only one patient (factitious disorder) among them fit the definition of FUO.

Among patients with prolonged fever who did not meet the definition of FUO, there was a considerable number of patients with critical illnesses that required more than 3 days of investigation until definitive diagnosis, such as intra-abdominal abscess, polymyalgia rheumatica, sarcoidosis, ulcerative colitis, Castleman's disease, hematological and solid malignancies, and panhypopituitarism.

Maximum body temperature, neutrophil count, and CRP levels were significantly higher in FUO patients than in patients not meeting FUO criteria for whom the cause of fever was not determined within 3 days of investigation. Furthermore, FUO patients displayed a longer duration from onset of fever to first visit (Table 3).

Patients without definitive diagnosis at discharge

A definitive diagnosis was not reached during hospitalization for 33 patients (14.6%). Possible diagnoses were given for 19 patients (57.6%) at discharge, although the likelihood of diagnosis did not seem to be >75% (Table 4). Drug-induced fever was the most common possible diagnosis (n=

4), followed by unspecified vasculitis that did not fit the concept of a specific vasculitis syndrome (n=2) and systemic viral infection (n=2). In the remaining 14 patients, clinicians had no idea about the cause of fever even after close examination in hospital. There was 1 patient who died during hospitalization without definitive diagnosis even after autopsy.

Follow-up of patients without definitive diagnosis

Adequate follow-up information was obtained from 28 of the 32 patients discharged alive without definitive diagnosis (87.5%). One patient died of esophageal cancer during the follow-up period. Fever had subsided during hospitalization, and this death was considered unrelated to the condition that had caused fever. A definitive diagnosis was eventually made in 7 patients, with 4 patients started on corticosteroid therapy for unspecified vasculitis (n=2), rheumatoid arthritis (n=1) and neuro-Behçet's disease (n=1). However, diagnosis for the 64-year-old man considered to have rheumatoid arthritis was eventually changed to ulcerative colitis. Cat-scratch disease had been suspected at discharge in the patient who was finally diagnosed with neuro-Behçet's disease, based on cervical lymph node biopsy findings. How-

Table 3. Comparison between FUO Patients and Patients not Meeting FUO Criteria for Whom the Cause of fever was not Determined Within 3 Days of Investigation*

	FUO	Non-FUO†	P-value
N	51	61	
Age, y	51 (34-71)	50 (25-68)	0.29
Women	25 (49.0)	32 (52.5)	0.85
Max. body temperature‡, °C	38.8 (38.5-39.6)	37.6 (37.2-38.1)	<0.001
Systolic blood pressure, mmHg	116 (104-130)	126 (115-142)	0.01
Diastolic blood pressure, mmHg	68 (60-80)	73 (63-80)	0.17
Heart rate, beats/min	86 (75-96)	84 (78-92)	0.73
Respiratory rate, breaths/min	20 (16-22)	18 (16-20)	0.22
White blood cell count, ×10 ³ /mm ³	7.0 (5.1-10.1)	6.2 (4.8-8.5)	0.17
Neutrophil count, ×10 ³ /mm ³	5.1 (3.5-6.9)	3.7 (2.7-5.6)	0.02
C-reactive protein, mg/dL	6.1 (2.5-11.9)	1.7 (0.2-7.9)	<0.001
Erythrocyte sedimentation rate, mm/h	66.5 (34-92)	50 (34-95)	0.62
Interval from onset to first visit‡, d	30 (17-150)	13 (4-47)	0.004
Interval from first visit to admission‡, d	4 (1-15)	3 (1-14)	0.59

Abbreviations: FUO, fever of unknown origin.

* Data are number (percentage) or median (interquartile range).

† Patients not meeting FUO criteria for whom the cause of fever was not determined within 3 days of investigation.

‡ Maximum body temperature documented in hospital or in the outpatient department.

§ Number of days between onset of fever and first visit to our outpatient department.

|| Number of days between first visit and admission.

ever, about 1 year after discharge, fever recurred and headache, sensory disturbance and weakness in the legs, and blurred vision developed. Then neuro-Behçet's disease was diagnosed. In the remaining 3 patients, the cause of fever was determined after discharge to be drug-induced fever (penicillin ; n=1), patella fracture (n=1) and recurrent fever associated with progesterone action (n=1). The 19-year-old man finally diagnosed as patella fracture was thought to be suffering from hereditary periodic fever at discharge.

In the remaining 21 cases without definitive diagnosis, fever subsided spontaneously. While 2 patients required rehospitalization due to recurrence of fever, neither encountered a relapse after second discharge. In the other 19 patients, fever disappeared during or shortly after hospitalization and never recurred.

Patient death during hospitalization

A total of 19 patients (8.4%) died during hospitalization. Age [median (interquartile range), 58 y.o. (48-68) vs. 49 (25-67); P=0.04], neutrophil count [$6.9 \times 10^3/\text{mm}^3$ (4.7-15.0) vs. 4.7 (3.2-7.3); P=0.04] and CRP levels [12.6 mg/dL (7.2-23.5) vs. 4.4 (0.8-10.9); P=0.001] were all significantly higher in deceased patients than in patients discharged alive.

Cause of fever could not be determined before death in 3 patients. A 30-year-old man was referred to our hospital with prolonged fever, myalgia in his legs, and elevations in plasma muscle enzymes. We made a tentative diagnosis of nonspecific myositis and corticosteroid therapy was started. However, severe acute pancreatitis developed, resulting in cardiopulmonary arrest. We could not determine any specific cause of the myositis even after autopsy. The other 2 patients were given a definitive diagnosis by autopsy. Cause of death in one patient was lung cancer, while the cause of fever was cholecystitis due to gall stones. In another patient, Sweet's syndrome involving the myocardium was diagnosed on autopsy.

Cause of fever was confirmed before death in the remaining 16 patients. All except 1 patient displayed malignant disease, with 1 case of Hodgkin's disease and 14 cases involving solid tumors. Among the 15 patients with malignant disease, fever was caused by the neoplasm itself in 7 cases.

Table 4. Possible Diagnoses in Patients Without Definitive Diagnosis at Discharge

Infections	
Systemic viral infection	2
Pharyngitis	1
Atypical mycobacterium infection	1
Spontaneous bacterial peritonitis	1
Appendicitis or Diverticulitis	1
Pelvic inflammatory disease	1
Chronic pyelonephritis	1
Cat scratch disease	1
NIID	
Vasculitis (unspecified)	2
Miscellaneous causes	
Drug-induced fever	4
Liver cirrhosis	1
Gastrointestinal bleeding	1
Hereditary periodic fever	1
Exaggerated circadian temperature rhythm	1

Abbreviation: NIID, noninfectious inflammatory diseases.

One patient without malignancy was diagnosed with pneumonia. This patient was an 87-year-old man who was immediately diagnosed with pneumonia following chest radiography taken on the first visit. During treatment with antibiotics, however, acute myocardial infarction and acute respiratory distress syndrome developed and the patient died.

Discussion

We reviewed and analyzed the medical records of 226 consecutive hospitalization episodes in the Department of General Medicine in Kyoto University Hospital with fever as one of the clinical problems. Although the majority of illnesses involved some sort of infection, NIID, particularly adult Still's disease and primary vasculitis syndromes, represented leading causes among patients meeting the definition of FUO. Tuberculosis, pyelonephritis, hematological malignancies and psychological disorders also tended to be associated with late diagnosis. However, few psychological disorders met the definition of FUO. Drug-induced fever, systemic viral infection and unspecified vasculitis were difficult to definitively diagnose even when suspected as a cause of fever. Follow-up of patients discharged without a definitive diagnosis revealed that none died of the illness causing fever after discharge, and long-term prognosis for the resolution of fever was good. Most patients who died during hospitalization displayed malignant disease.

The results of the current analysis had much in common with those of previous studies on FUO. First, the findings regarding the change in timing for diagnosis, with infections more prevalent in the early-diagnosis group and NIID more prevalent in the late-diagnosis group, are similar to the findings from a study by Vanderschueren et al (6). This reflects the fact that most infections can be diagnosed from simple diagnostic tests such as chest radiography and urinalysis,

while diagnosis of NIID requires more invasive procedures such as biopsy or a combination of various diagnostic findings to meet the diagnostic criteria. Second, the results from follow-up of 28 patients who had no definitive diagnosis at discharge agreed with results from prior studies in which patients with undiagnosed FOU were followed-up after discharge (6, 7). Since all 28 patients were either properly treated after obtaining definitive diagnosis or spontaneously defervesced, careful ambulatory follow-up clearly represents a reasonable strategy for stable undiagnosed cases, in contrast to an aggressive in-hospital evaluation. Third, as Larson et al argued in their study on FOU that disease categories and age were predictors of survival (8), as many as 84% of the patients (16/19) who died during hospitalization displayed malignancy, regardless of whether this was the cause of fever, and patients who died were significantly older than survivors in the present study.

Although the present definition of FOU is well suited to the exclusion of prolonged fever caused by psychological problems, we identified a considerable number of critical illnesses among patients who did not strictly fulfill the definition. Even for the diagnosis of psychological disorders, clinicians have to make a careful examination in an effort to rule out critical organic disorders. Therefore, the diagnostic approach applied in the workup of FOU should also be used in all patients with prolonged fever.

The present findings have some limitations. First, since the present study was based on a review of medical records, not all relevant information was clearly recorded. For example, the day on which the definitive diagnosis was established was not easy to determine in some patients. In addition, the determination of diagnosis was problematic in cases where several possible diagnoses were suggested and some doubt existed regarding the diagnosis established during hospitalization. To resolve such problems, we often discussed with each other and consulted clinicians who had directly cared for the patients during hospitalization. A second problem was the lack of generalizability. Since the present study was conducted in a tertiary university hospital, our findings are not readily applicable to patients in community hospitals.

Conclusions

The present findings for all febrile patients at hospitalization displayed common results as the findings of prior FOU series. There are a considerable number of critical illnesses among patients who do not strictly fulfill the present definition of FOU. Therefore, strict use of the definition of FOU is unwarranted when managing patients with prolonged fever.

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