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Fever of Unknown Origin (FUO)

I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria

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Introduction

Fever of unknown origin (FUO) is a challenging medical problem. Petersdorf and Beeson (30) defined FUO as an illness characterized by rectal temperature exceeding 38.3 °C on at least 3 occasions, evolving during at least 3 weeks, with no diagnosis reached after 1 week of inpatient investigation. Many retrospective (2, 4, 5, 12, 15, 18, 20, 28, 32, 34, 35) and a few prospective (1, 16, 19, 23, 25) studies of patients with FUO have been performed using this definition. Other series have used different criteria (3, 9-11, 14, 17, 21, 24, 27, 31, 33, 36), and their results are more difficult to interpret. A more recently revised definition (8, 23, 29) that excludes immunocompromised patients has not been employed in major series yet.

The spectrum of diseases causing FUO not only seems to be determined by geographical factors, but also appears to change with time. In recent series, the proportion of patients in whom no diagno-

sis was made has increased compared with older series (23, 28). In addition, comparison is troublesome because, on the one hand, most studies do not use uniform epidemiologic entry criteria, thus possibly introducing unintended bias, and, on the other hand, differences in diagnostic workup can influence the outcome. Consequently, uniform entry criteria and continuous auditing for completeness are necessary, and a standardized diagnostic workup is preferable.

To update information on FUO and incorporate these new ideas, we conducted a prospective, 2-year study on patients with FUO in all 8 Dutch university hospitals, in which we excluded immunocompromised patients and used a standardized protocol to minimize diversity in diagnostic management. This protocol was based on retrospective analysis of diagnostic management (5) and an in-depth inquiry into diagnostic management among internists in the 8 Dutch university hospitals (6).

Methods

The present study was undertaken from January 1992 to January 1994. Because we wanted to enroll all admitted patients fulfilling criteria for FUO, without any unintended selection bias, 2 very broad initial selection criteria were used. First, all records of nonimmunocompromised patients with fever on the internal medicine wards in all 8 university hospitals in the Netherlands were reviewed for the Petersdorf criteria for FUO once a week (illness characterized by rectal temperature exceeding 38.3 °C, evolving during at least 3 weeks, with no diagnosis after 1 week of inpatient investigation). Total bed capacity of each of the 8 university hospitals ranged from 715 to 1,260 beds. Immunocompromised patients were considered patients with neutropenia for at least 1 week within 3 months before the onset of fever (white blood cell count $< 1.0 \times 10^9/L$ and/or granulocyte $< 0.5 \times 10^9/L$); human immunodeficiency virus (HIV)-positive patients; patients with known hypogammaglobulinemia (IgG $< 50\%$); and patients using the equivalent of more than 10 mg prednisone for at least 2 weeks. Second, as an additional check, all blood culture orders were reviewed weekly at the microbiologic laboratory, and the records of the patients in whom blood cul-

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Abbreviations used in this article: CT, computed tomography; FUO, fever of unknown origin; NIID, noninfectious inflammatory diseases; PDCs, potentially diagnostic clues.

tures were ordered were reviewed. The latter procedure was added because in a retrospective study (5) we found that in all patients with FUO, blood cultures were performed. After thus having identified all patients with fever, we applied the Petersdorf and Beeson criteria (30), as described above. By combining these 2 methods, we minimized the chance of missing patients who fulfilled FUO criteria.

The study was approved by all local ethic committees. After informed consent, patients were included in our FUO protocol, which consisted of a standardized precoded history and standardized thorough physical examination. As a minimum, several additional investigations had to be performed in the first week of admission (Table 1). Much weight was given to the presence or absence of potentially diagnostic clues (PDCs), defined as all localizing signs, symptoms, and abnormalities potentially pointing toward a possible diagnosis, and the use of these PDCs in the diagnostic process. False PDCs are defined as PDCs eventually not leading to the definite diagnosis. History, physical examination, laboratory and technical investigations, the presence of PDCs, and their use in the diagnostic process were prospectively registered in a structured data collection form. If PDCs were present, appropriate investigations were performed. If PDCs were absent or false only, patients underwent a standardized diagnostic protocol (see Table 1).

TABLE 1. Diagnostic protocol

Obligatory investigations performed in all patients

Sedimentation rate; hemoglobin; mean cellular volume; platelet count; leukocyte count and differential count; serum urea nitrogen; creatinine; sodium; potassium; protein; protein fractions; alkaline phosphatase; aminotransferase; lactate dehydrogenase; creatine phosphokinase; antinuclear antibodies; rheumatoid factors; urinary analysis; feces for occult blood; blood cultures aerobic and anaerobic (n = 3); tuberculin test; urine, feces, and sputum culture when indicated; chest X-ray; ultrasonography of upper abdomen

Phase 1 diagnostic protocol in patients without PDCs (n = 5) or with misleading PDCs only (n = 38)

Pulse/rectal temperature measurement by observer; fundoscopy by an ophthalmologist; calcium, phosphate, urate, amylase, and TSH/T4; immunoelectrophoresis of serum and urine; CRP; ACE; ANCA; anti-dsDNA; ASO; cryoglobulin; C3, C4, CH50; serology for Cytomegalovirus, Epstein-Barr virus, *Mycoplasma*, *Brucella*, *Toxoplasma*, *Borrelia*, *Coxiella*, *Treponema*, *Yersinia*; blood cultures incubating > 1 week; blood cultures, gastric fluid, urine cultures for tuberculosis; stools for worms, eggs, cysts; bone marrow puncture and culture for *Mycobacteria*, *Brucella*, *Yersinia*; In-111-IgG scintigraphy; X-Ray of sinus and teeth; ultrasonography of pelvis

Phase 2 diagnostic protocol in patients without PDCs

(Performed when Phase 1 did not reveal PDCs or diagnosis)
Hepatitis B serology; anergy tests; repeated chest X-ray; IgD in serum; liver biopsy and culture for *Mycobacteria* and other bacteria and fungi; crista biopsy and culture for *Mycobacteria*, *Brucella*, and common bacteria; echocardiography; CT of abdomen and chest; X-Ray colon; temporal artery biopsy in patients over 55 years

Abbreviations: TSH = thyroid-stimulating hormone; T4 = thyroxine; CRP = C-reactive peptide; ACE = angiotensin-converting enzyme; ANCA = antineutrophil cytoplasmic autoantibodies; dsDNA = double-stranded deoxyribonucleic acid; ASO = antistreptolysin O test; C = complement; CH50 = total hemolytic complement; In-111-IgG = indium-111-labeled polyclonal human immunoglobulin G; CT = computed tomography; PDCs = potentially diagnostic clues.

Within 1 week of inclusion in the study, every patient was seen by the first author in order to streamline the management of the patients. Patients did not have to remain admitted; after inclusion all investigations of the protocol could be performed on an outpatient basis. The patient's clinical condition was the major reason for a longer stay in the hospital, at the discretion of the attending physician. The final diagnosis was established by the attending physician and the first author. Definite diagnoses were established by positive serology, cultures, or histology. In some patients probable diagnoses were established by excluding other disease, by the response to specific therapy, or by studying the course of the disease. A long follow-up was deemed indispensable for all patients in whom a final definite diagnosis could not be made. A final follow-up was therefore performed more than 2 years later in March 1996, by analysis of the records of the patients, telephone calls to the treating physicians, and, in some cases, telephone calls to the patients themselves.

Recurrent fever was defined in this study as at least 2 episodes of fever, with intervals of at least 48 hours without fever. Data were statistically analyzed and groups of patients compared with use of the Fisher exact test. A p value of <0.05 (2-sided) was considered significant.

Results

Clinical features

During the 2-year period of study, 167 patients (80 male, 87 female) met the criteria for FUO. The median age was 53 years (range, 16–87 yr); 46 patients (28%) were older than 65 years. Of these patients, 139 patients were found by reviewing weekly the records of all patients with fever; in all of these patients blood cultures were done. By means of blood culture surveys an additional 28 patients were retrieved that fulfilled FUO criteria and were not recognized as such when checking the records.

Sixty-five (39%) patients were referred by general practitioners and 64 (38%) had already undergone extensive investigations before referral to a university hospital, whereas 7 patients (4%) were referred by other departments within the university hospitals, and 31 patients (19%) were already known with other nonfebrile conditions at the university department. The proportion of patients in whom no diagnosis could be made was slightly lower, albeit not significantly, for patients referred by general practitioners (26%) than for secondarily referred patients (33%). For the 117 patients with a diagnosis, a diagnosis was established after a median of 60.5 days from the onset of fever (range, 21–1,584 d) in those referred by general practitioners, whereas in patients referred by non-university hospitals it took a median of 166 days (range, 22–3,347 d) (p = 0.005).

Median overall follow-up after admission was 854

days (range, 10–3,387 d). In 30 patients (18%) follow-up was less than 0.5 years. Fifteen of these 30 patients died within this period, only 1 of them without a diagnosis. In the other 15 patients, diagnosis was proved in 14 patients. One patient with probable venous thrombosis as the cause of her fever could not be traced during follow-up. The median follow-up of 50 patients without a diagnosis and 48 patients with a probable diagnosis was 1,080 days (range, 15–3,387 d). In only 3 of these 98 patients was follow-up less than 1 year.

Median duration of hospitalization was 27 days (range, 7–295 d). The median duration of fever in the group of 117 patients in whom a diagnosis was made was 78.5 days (range, 21–8,804 d). Of the 50 (30%) patients in whom no diagnosis was made, 37 patients recovered spontaneously after a median of 190 days (range, 30–13,844 d). Thirteen patients remained febrile; these patients had a median duration of fever of 1,021 days (range, 481–5,281 d). Except for 1 patient, patients with persistent fever all had some form of recurrent fever.

Recurrent fever was present in 56 patients. In 28 of those patients (50%), no diagnosis could be established, in contrast to 22 of 111 patients (20%) with continuous fever ($p < 0.0001$).

In 67 patients the fever lasted longer than 6 months. In 37 (55%) patients no diagnosis could be made, in contrast to 18 of 100 (18%) patients with fever lasting less than 6 months ($p < 0.0001$).

Diagnosis and outcome

In the 117 patients in whom a diagnosis was made, the diagnostic phase in the university hospital (after referral) took a median of 33 days (range, 1–1,297 d). In 42 patients the diagnosis was made after discharge during follow-up because of new emerging facts. Of the 167 patients in this series, 20 patients died during follow-up: in 18 of them a diagnosis was made, in 4 not until after autopsy. All but 1 patient succumbed to the disease responsible for the FUO. Infections were found in 43 (26%) patients, neoplasms in 21 (13%), and noninfectious inflammatory diseases in 40 (24%) patients (Table 2).

Infections: In 4 patients, **abscesses** were the cause of fever. In 2 patients these were **liver abscesses**, caused in the first patient by *Escherichia coli*, *Proteus mirabilis*, and *Bacteroides fragilis*, while in the second patient the abscess was culture negative at autopsy after empirical antibiotic therapy. The delay of diagnosis in these patients was due to inconclusive ultrasound examinations. In the first patient, the second ultrasonography revealed multiple abscesses in the liver; in the other patient a biopsy of the liver yielded the diagnosis.

In the last 2 patients **pelvic abscesses** were the cause of fever, caused in 1 patient by *Peptococcus species*, and in the other patient by *Escherichia coli* and *Streptococcus milleri*. In these patients the delay was due to failure to order pelvic ultrasonography because of the absence of lower abdominal pain.

There were 2 patients with **pleural empyema**. In 1, the chest radiography was incorrectly interpreted, resulting in a delay in the diagnosis. Scintigraphy and thoracic computed tomography (CT) led to the diagnosis, and culture of pleural fluid grew *Peptococcus species*. In the second patient, pleural fluid cultures were sterile, but pleural biopsies yielded *Actinomyces species*.

In 5 patients **urinary tract infection** turned out to be the cause of fever; 2 of them received antibiotics for other presumed infections at the time of the first urine culture. In both patients, urine cultures yielded *Klebsiella pneumoniae* eventually. In the third patient, recurrent prostatitis was found by transrectal sonography, and culture of prostatic secretion yielded *Klebsiella pneumoniae*. In the fourth patient, chronic xanthogranulomatous pyelonephritis with obstruction of the ureter was demonstrated by abdominal CT; cultures of urine and blood remained negative. In the fifth patient, balanitis accompanied the urinary infection, cultures yielded *Escherichia coli*, and, after circumcision, fever subsided.

Endocarditis was found in 4 patients. Culture-negative endocarditis occurred in 2 patients, and the diagnosis was not made until autopsy by histology. In 1 of these 2 patients echocardiography had been negative, in the other echocardiography was not performed, because false PDCs were present. In the third patient, cultures became positive for *Streptococcus bovis* when empiric antibiotic therapy was stopped. In the fourth patient, blood cultures were not drawn in the referring hospital and empirical antibiotics were given. Because of deterioration the patient was referred to our hospital, and 2 days later blood cultures yielded *Staphylococcus aureus*.

In 6 patients a clinical picture of **pneumonia** was present. In all patients chest X-rays showed segmental infiltrates consistent with bronchopneumonia. In 3 patients bronchoscopy with culture of bronchial fluid and serology for respiratory viruses, *Chlamydia*, *Legionella*, *Mycoplasma pneumoniae*, and *Coxiella burnetii* were negative and thus no causative microorganism could be found. The first patient also had mediastinal lymphadenopathy and some pleural effusion and had already received extensive antibiotic therapy (cephalosporin, amoxicillin, flucloxacillin, and tobramycin) elsewhere without disappearance of

TABLE 2. Final diagnoses in 167 patients with fever of unknown origin

Diagnostic Category	No. of Patients	(%)
Infections	43	(25.7)
Bacterial*		
Abscess/lung empyema†	6	
Urinary tract infections	5	
Endocarditis	4	
Atypical or recurrent pneumonia	6	
Tuberculosis	3	
Other bacterial infections	12	
Viral		
Cytomegalovirus infection	5	
Other viral infections*	2	
Fungal		
Disseminated cryptococcal infection	1	
Neoplasms*	21	(12.6)
Hematologic	14	
Solid	7	
Noninfectious inflammatory diseases	40	(24.0)
Collagen diseases	19	(11.4)
Adult-onset Still disease*	6	
Mixed cryoglobulinemia	5	
Other*	8	
Vasculitis syndromes	14	(8.4)
Temporal arteritis	4	
Other*	10	
Granulomatous diseases	7	(4.2)
Inflammatory bowel diseases	2	
Sarcoidosis	2	
Other*	3	
Drug fever	3	(1.8)
Factitious fever	2	(1.2)
Miscellaneous*	8	(4.8)
No diagnosis	50	(29.9)
Spontaneous recovery	37	
Persistent fever	13	

*See Results Section for details.

†One patient with urinary tract infection also.

fever. After referral, he recovered spontaneously after 8 weeks of fever. The second patient had received doxycycline, amoxicillin, gentamicin, cephazolin, and erythromycin without improvement of his condition. Isoniazid, rifampin, and pyrazinamide were given for 6 weeks without effect and stopped when cultures for tuberculosis remained negative. He recovered spontaneously over a 6-month period thereafter. The third patient was treated with penicillin, erythromycin, and rifampin for 4 weeks; after this period the patient's temperature was below 38 °C, antibiotic therapy was stopped, and the patient recovered further during the next 2 weeks. In the fourth patient with pneumonia, *Haemophilus influenzae* and *Stenotrophomonas maltophilia* were cultured first; after antibiotic therapy with cefuroxime, fever persisted. A second culture after stopping therapy revealed *Moraxella catarrhalis*; antibiotic therapy with amoxicillin-clavulanate was successful. In the fifth patient, *Pseudomonas aeruginosa* was cultured. She was treated with ceftazidime intravenously, but fever persisted. Because of a

history of tuberculosis in the past, she was then treated with isoniazid, pyrazinamide, and rifampin without result. Repeated bronchoscopic examination and culture of bronchial fluid yielded *Pseudomonas aeruginosa* again. After several weeks of therapy with ciprofloxacin, she recovered. In the sixth patient with pneumonia, *Haemophilus influenzae* and *Stenotrophomonas maltophilia* were cultured. Erythromycin had already been given empirically without any effect, and ciprofloxacin was added. By then *Klebsiella pneumoniae* had been cultured from the urine also. We concluded that this patient had 2 different infections causing the FUO. It took more than 20 days for her to recover and her temperature to normalize.

Tuberculosis was proved in 3 patients by culture. In the first patient, pericardial puncture revealed the diagnosis. In the second patient, a positive purified protein derivative (PPD) test and erythema nodosum suggested tuberculosis, but no localization seemed present after inclusion. A somatostatin scintigraphy was performed which showed activity high in the axilla. An ultrasono-

graphic biopsy of enlarged axillary lymph nodes showed acid-fast bacilli. Cultures grew *Mycobacterium tuberculosis*. The third patient had a recent history of breast cancer and bone metastasis, and lymphangitis carcinomatosa was suspected. Corticosteroids were administered empirically. Because of deterioration and in accordance with the diagnostic protocol, sputum cultures for tuberculosis were performed, which showed acid-fast bacilli. Cultures grew *Mycobacterium tuberculosis* eventually.

Cytomegalovirus infection was proved in 5 patients by serology (a fourfold elevation of IgG titer); in all but 1 patient lymphocytosis and atypical lymphocytes in the blood smear were found initially but false PDCs delayed the diagnostic process.

Other bacterial infections included persistent *Yersinia enterocolitica* infection (n = 2), diverticulitis (n = 2), recurrent sinusitis, cholangitis, adnexitis, bacterial meningitis in ventriculo-peritoneal drain with *Escherichia coli*, typhoid fever, occult dental infection, secondary syphilis, and infected central venous device with *Staph. epidermidis* and *Staph. aureus*.

Neoplasms: In 14 patients **hematologic malignancies** were found. Hodgkin disease was the cause of fever in 5 patients. In 2 patients, the diagnostic process was delayed because their fevers were erroneously attributed to previously diagnosed diseases (systemic lupus erythematosus and sarcoidosis). In 2 others there was no lymphadenopathy, and diagnosis was made by bone marrow biopsy. In the fifth patient there was only mediastinal localization of Hodgkin disease. In 4 patients non-Hodgkin lymphomas were the cause of fever. In the first of these patients, very small abdominal lymph nodes were found by abdominal CT, 3 years after successful allogeneic bone marrow transplantation. Positive yersinia serology (Western blot) delayed diagnostic laparotomy in a second patient with abdominal lymphadenopathy. The third patient had a 3-year history of recurrent fever. Only misleading PDCs were present during first admission in the university hospital, and, because fever subsided, the standardized diagnostic protocol was not used. During the next episode of fever, anemia developed and bone marrow biopsy revealed non-Hodgkin lymphoma. The fourth patient had an 18-year history of progressive polyneuropathy, telangiectasis, muscle weakness, hepatomegaly, and lymphadenopathy. Despite a large series of extensive investigations, a diagnosis was never established. She had never been febrile before inclusion in our study, when a malignant T-cell tumor was identified. Other hematologic malignancies were angio-immunoblastic lymphoma (n = 2), acute

leukemia, acute myelofibrosis, and gamma-heavy-chain disease (Franklin disease).

In 7 patients a variety of **solid tumors** was responsible for the fever. Primary tumors were found in 2 patients, 1 with breast cancer and 1 with stomach cancer. Metastasis of breast cancer (n = 2), larynx cancer, and adenocarcinoma of unknown origin were found in 4 other patients. In the seventh patient, necrosis of a dermoid tumor in Gardner syndrome was responsible for the FUO.

Noninfectious inflammatory diseases

—**Collagen diseases:** The diagnosis of adult-onset Still disease was made in 6 patients. All patients met the Medsger and Christy criteria for adult-onset Still disease (26), but the diagnosis was made only after prolonged observation and exclusion of other diseases. Other collagen diseases found in this series were mixed cryoglobulinemia (n = 5), systemic lupus erythematosus (n = 2), reactive arthritis (n = 2), polymyalgia rheumatica (n = 1), relapse of polymyositis (n = 1), dermatomyositis (n = 1), and relapse of rheumatoid arthritis (n = 1).

—**Vasculitis syndromes:** Temporal arteritis was found in 4 patients. Other vasculitis syndromes found in our series were hypersensitivity vasculitis (n = 3), polyangiitis overlap syndrome (n = 2), and Wegener disease (n = 2); Schnitzler disease (urticarial vasculitis with monoclonal IgM), vasculitis accompanying rheumatoid arthritis, and polyarteritis nodosa were found in 1 patient each.

—**Granulomatous diseases:** Two patients had inflammatory bowel diseases, and 2 patients had sarcoidosis. In 2 patients granulomatous hepatitis was found, and in 1 patient granulomatous myositis was found, without underlying disease as cause of the fever.

Miscellaneous diseases: The miscellaneous group encompassed aseptic meningitis (Mollaret meningitis) without underlying disorders (n = 2); pseudogout (n = 2); and gout, venous thrombosis, hyperthyroidism, and allergic pneumonitis after radiation therapy, found in 1 patient each.

Diagnostic process

PDCs were present in 162 (97%) patients. The 10 most common PDCs were relevant diseases in past (131 patients), weight loss (93 patients), relevant operation in past (68 patients), headache (62 patients), myalgia (58 patients), diarrhea (50 patients), vertigo (48 patients), arthralgia (48 patients), heart murmur (41 patients), pulmonary abnormalities (38 patients). These PDCs led to the diagnosis in 101 patients (62%). In 48 of these 101 patients, false PDCs were also present. In 13 patients a diagnosis was

made despite the presence of false PDCs only. No clues were present in 5 patients, in 2 of whom no diagnosis was made. There was a small but not significant difference in reaching the diagnosis between patients with clues (73%) or patients without clues (60%).

In 16 patients without PDCs or with false PDCs only, diagnoses were made with the help of the standardized diagnostic protocol. More detailed information on PDCs and the use of the diagnostic protocol is found in our companion article (6a) later in this issue.

Discussion

In this prospective multicenter study of 167 patients, FUO was due to infection in 26% of patients, neoplasms in 13%, noninfectious inflammatory diseases (NIID) in 24%, and miscellaneous causes in 5%, whereas the diagnosis was not established in 30% of patients despite every effort. This is in agreement with the findings of our retrospective study in a single institution (5) and those of other recent series (23, 28), but in contrast to older reports (Table 3). There are a number of possible explanations for this phenomenon. First, 38% of patients were referred after undergoing extensive investigations elsewhere, comparable to the findings of Knockaert et al (28%) (23). In most series of FUO in the literature, exact data on referral patterns are lacking (1, 15, 25, 30, 32, 34). One could speculate that more difficult-to-diagnose cases are referred, with a lower chance of reaching a final diagnosis. In our series however, the proportion of patients without a diagnosis was only slightly higher in the referred group. It is more likely that the introduction of advanced diagnostic techniques had a major impact. In many patients who formerly would have been classified as having FUO because of difficulty in reaching a diagnosis, a diagnosis now is likely to be established. This is especially true for disease enti-

ties such as endocarditis, abdominal abscesses, and malignant lymphoma that can be diagnosed easily by ultrasonography, a technique used very early in the diagnostic process now. This leaves us with a group of patients fulfilling classical criteria, in whom a diagnosis is much more difficult to make with mostly self-limiting or benign fevers. There has also been a shift in diseases that cause fever. For instance, in nonimmunocompromised patients, tuberculosis has become relatively rare. Many infections in our series were due to common microorganisms. Petersdorf and Beeson (30) excluded these disorders because they represented common entities, but it is important for attending doctors to realize that FUO can be caused by such common diseases and microorganisms, which might be concealed by false PDCs or the use of antibiotics.

Compared with results of other series from university hospitals (20, 28, 30), tumors were not a common cause of FUO in the present study. This is in agreement with our retrospective survey and 1 other recent series (15, 23). This could be the result of the widespread use of advanced diagnostic techniques early in the diagnostic process—for instance, ultrasonography, computed tomography, and serologic techniques. As expected, some hematologic malignancies remain difficult to diagnose because of the lack of localizing symptoms. Metastases can be very small, while causing FUO and other paraneoplastic symptoms (7). The diagnostic process in patients with a history of malignancy should be focused on recurrence of the tumor.

In contrast to other series, we used a dual method to find cases. In this way, all patients that presented with FUO were retrieved. It is of interest that 3 of the 6 prospectively conducted studies on FUO did not mention the way in which cases were retrieved (1, 25, 30), and methods in the other 3 studies (2, 16, 25) still show a degree of selection bias because no control system was used to avoid missing patients fulfilling FUO criteria. Of course,

TABLE 3. Diagnostic categories in fever of unknown origin, previous and present studies (%)

Diagnostic Category	Older Major Series			New Series	
	Ref. 30 1961 (n = 100)	Ref. 25 1982 (n = 105)	Ref. 2 1984 (n = 133)	Ref. 23 1992 (n = 199)	Present Study (n = 167)
Infections	36	30	32	22.7	25.7
Neoplasms	19	31	20	7.0	12.6
Noninfectious inflammatory diseases	19	15	16	23.1	24.0
Collagen diseases	(13)	(5)	(3)	(8.5)	(11.4)
Vasculitis syndromes	(2)	(4)	(11)	(10.6)	(8.4)
Granulomatous diseases	(4)	(8)	(2)	(4.0)	(4.2)
Drug fever	1	0	0	3.0	1.8
Factitious fever	3	3	4	3.5	1.2
Miscellaneous	15	8	7	15.1	4.8
No diagnosis	7	13	21	25.6	29.9

serious selection bias cannot be prevented in retrospective studies.

In accordance with the suggestions made by Durack and Street (8) and Petersdorf (29) we excluded immunocompromised patients with FUO, because these patients show an entirely different spectrum of diseases causing fever. One of the criteria for FUO is admission to hospital for 1 week, without a diagnosis being established. This is a time-related criterion, which may cause important differences as it is dependent on the experience of the doctor, the facilities, and differences in management between countries or even hospitals. The differences that can be caused by this criterion make comparison between different series difficult. In our opinion, the recommendation of Knockaert et al (23) and Durack and Street (8) to shorten this period to 3 days is not an improvement, for several reasons. First, a better way to reduce bias is to change from a time-related criterion to a quality-related criterion that requires a list of certain investigations to be performed, as a minimum. We have used such a list (see Table 1). One could add directional investigations based on PDCs, performed within the first week of admission. Second, the major reason to classify patients with FUO as such is to indicate that we deal with a difficult or potentially difficult problem. In that context, maintaining the criterion of 1 week of clinical analysis seems appropriate to us, but perhaps in this regard a difference in admission policy between the Netherlands and the United States plays a role. Third, it is our experience that 3 days is often too short to exclude diseases that are easy to diagnose, because the results of cultures and serology often take more than 2–3 days.

Even if the criteria are adapted, comparing series of patients with FUO remains troublesome. Geographic factors (18, 32, 35), age distribution of the study population (11), referral pattern, hospital setting (16, 20), and time and duration of study (changes in disease pattern and diagnostic management) influence the distribution of diagnostic categories. Selection bias increases when patients with FUO presenting at the outpatient department are included; prospective case finding is much harder to realize, and standardized diagnostic protocols are more difficult to implement. It would, however, be instructive to study this group of patients with a standardized protocol.

The median duration of hospitalization and of diagnostic phase was 27 days and 33 days, respectively. These figures are in accordance with figures presented by Knockaert et al (25 and 19 days, respectively) (23) and by our retrospective study (a median of 23 days of hospitalization) (5). In most other major series no such data are presented. In a

review of patients with FUO in community hospitals, Kazanjian (20) found that it took a median of 19 days to establish a diagnosis after a median duration of hospitalization of 11 days. It is possible that the difference between these data indicates a difference between the degree of difficulty of the patient groups.

The chance of reaching a diagnosis in patients with recurrent fever and fever lasting longer than 6 months is relatively low. This was also found by Knockaert et al (22).

Different nomenclature for the group of patients without infections or neoplasms has been used in series on FUO. Terms used include "rheumatic diseases," "multisystem diseases" (23), "dyscollagenosis" (4, 35), "collagen diseases" (12, 15, 18, 30), "collagen vascular diseases" (1, 2, 13, 19, 20, 25), "connective tissue diseases" (16, 32, 34), and "inflammatory disorders" (8). Most series of FUO distinguish a category of diseases labeled as "collagen disorders," which includes vasculitis and autoimmune diseases. Since collagen is involved in only a few of these disorders, and an autoimmune nature is often difficult to prove, we would break a lance for using the term "noninfectious inflammatory diseases" (NIID) in the future. This category could also include granulomatous disorders, like inflammatory bowel disease and sarcoidosis, usually listed under miscellaneous disorders. A subdivision as presented in Tables 2 and 3 still allows for comparison with older series. NIID accompanied by fever are often classified as FUO. In these diseases, fever may precede more typical manifestations or serologic evidence by months. Moreover, many of these diseases can only be diagnosed after prolonged observation and by exclusion.

Summary

Internal medicine wards in all 8 university hospitals in the Netherlands participated in this prospective study of fever of unknown origin (FUO) from January 1992 until January 1994 in order to update information on the spectrum of diseases causing FUO.

We used fixed epidemiologic entry criteria to achieve completeness of enrollment and to avoid unintended selection bias. After entry, immunocompetent patients were included using criteria for FUO according to Petersdorf and Beeson (30). A standardized diagnostic protocol was used, and potentially diagnostic clues (PDCs) and their use in the diagnostic process were prospectively registered. Thus, the criteria of classic FUO have been adjusted to modern times: immunocompromised patients are excluded, and the time-criterion "1 week in hospital

without a diagnosis" has been replaced by a quality-criterion stating that certain investigations must be performed as a minimum, and PDCs must be followed adequately for at least 1 week, without a diagnosis being reached.

A total of 167 immunocompetent patients with FUO were thus retrieved, of whom 43 (25.7%) had infections, 21 (12.6%) had neoplasms, and 40 (24.0%) had noninfectious inflammatory diseases. No diagnosis was made in 50 patients (29.9%), 37 of whom recovered spontaneously.

This study confirms the changing spectrum of diseases causing FUO. Indeed, as shown by another recent study, the group of patients with FUO in whom no diagnosis can be made is expanding, and mostly it concerns self-limiting or benign fevers. Others have suggested that this trend is not really occurring (29). We did not place patients with diseases of unknown origin in the "nondiagnosis" group, and indeed made presumptive diagnoses when necessary. Nevertheless, this category of undiagnosed fevers is increasing. We believe that the higher percentage of undiagnosed cases can be attributed to the greater use of advanced diagnostic techniques attendant on an increased number of self-limited illnesses in patients meeting criteria for FUO. Because of ongoing development in diagnostic techniques and the prospective influence on the spectrum of diseases causing FUO, studies should be performed regularly to update information on this subject. Because the number of outpatient evaluations for FUO is expected to increase, patients seen on an outpatient basis should be included in future studies. To avoid unwanted selection bias, fixed epidemiologic entry criteria should be used to ensure completeness of enrollment. To shorten the period of collecting data, multicentric studies can be done using standardized diagnostic protocols.

In patients with recurrent fever or fever lasting longer than 6 months, the chance of reaching a diagnosis is significantly lower, and especially in this group one should exercise the greatest caution to avoid abundant and extensive diagnostic procedures.

The diagnostic process in patients with FUO remains an intriguing problem in medicine. Recent microbiologic techniques may be useful as an approach to the relatively large proportion of patients in whom we now fail to make a diagnosis.

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