Fever of unknown origin in the 2000s: Evaluation of 103 cases over eleven years

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Summary

Purpose > Despite recent diagnostic advances, a fever of unknown origin (FUO) remains a clinical challenge.
Methods > This study reports the clinical courses and outcomes of 103 cases of FUO and evaluates the places of ^{18}F-Fluorodeoxyglucose positrons emission tomography ([18]FDG-PET) and molecular biology in the diagnostic approach.
Results > This retrospective study was carried out from 2002 to 2012 in two departments of internal medicine. The diagnosis of FUO was based on the updated criteria of Durack and Street. It included 54 men and 49 women (mean age: 57 years) in 52 of whom the final diagnosis could not be established. Among the 51 patients with final diagnosis, non-infectious inflammatory disorders were the most prevalent (61%). The other diagnoses were infectious diseases (23.5%), miscellaneous causes (10%) and malignancies (6%). [18]FDG-PET was performed in 48 patients and was contributory in 10. Molecular biology techniques were performed in 28 patients and were contributory in only one case: detection of a cytomegalovirus infection by polymerase-chain-reaction assay. At study closure, eleven patients had died, of whom five died from the disease that

Résumé

Évolution des fièvres prolongées inexpliquées depuis 2000 : évaluation de 103 cas

Objectif > Malgré les progrès diagnostiques récents, une fièvre d'origine inexpliquée (FOI) demeure un défi pour le clinicien.
Méthodes > Cette étude porte sur l'analyse de 103 cas et évalue l'apport de la tomographie par émission de positons au 18F-Fluorodésoxyglucose ([18]FDG-PET) et de la biologie moléculaire dans la démarche diagnostique.
Résultats > Cette étude rétrospective a été menée de 2002 à 2012 dans deux départements de médecine interne. Le diagnostic de FOI a été basé sur les critères actualisés de Durack et Street. Elle comprenait 54 hommes et 49 femmes (âge moyen : 57 ans) dont 52 chez qui le diagnostic final n'a pu être établi. Parmi les 51 patients avec diagnostic final, les maladies inflammatoires non infectieuses étaient les plus répandues (61 %). Les autres diagnostics étaient les maladies infectieuses (23,5 %), des causes diverses (10 %) et les tumeurs malignes (6 %). Une [18]FDG-PET a été réalisée chez 48 patients et a été contributive chez 10 d'entre eux. Les techniques de biologie moléculaire ont été réalisées chez

caused the FUO. Only two deaths among the 52 patients without diagnosis could be attributed to the feverish illness.

Conclusion > As observed in the most recent case series, the rate of undiagnosed patients is increasing. The prognosis was good for undiagnosed FUO. Here, the yield of [18]FDG-PET was 21% but that of molecular biology negligible. The recourse to molecular biology seems useless unless directed by a high degree of clinical suspicion.

28 patients et ont été contributives dans un seul cas : la détection d'une infection à cytomégalovirus par PCR. Sur la durée de l'étude, onze patients sont décédés, dont cinq de la maladie responsable de la FUO. Seuls deux décès parmi les 52 patients sans diagnostic pouvaient être attribués à la « maladie fébrile ».

Conclusion > Comme cela a été observé dans les études les plus récentes, le taux de patients non diagnostiqués est en augmentation. Le pronostic est bon pour les FOI sans diagnostic. Ici, le rendement de [18]FDG-PET était de 21 %, mais celui de la biologie moléculaire négligeable. Le recours à la biologie moléculaire semble donc inutile sauf si orienté par un haut degré de suspicion clinique.

In 1961, Petersdorf and Beeson defined fever of unknown origin (FUO) as an illness of more than three weeks duration, with fever higher than 38.3 °C on several occasions, the cause of which remains uncertain after a week of in-hospital investigation [1]. Thirty years later, Durack and Street [2] suggested two major changes:

- distinction between classical FUO and other types; e.g., nosocomial FUO, neutropenic FUO, or HIV-associated FUO;
- a reduced duration of investigation: i.e., three outpatient visits or three days of in-hospital investigation.

The 3-day period is the time needed for classical cultures or skin tests to reveal a positive or negative result whereas the required imaging can be performed in one day or after one outpatient visit. Currently, it is agreed that despite its limited performance, chest and abdomino-pelvic computed tomography (CT) remains the reference examination in replacement of the combination chest radiography + abdominal ultrasound [2]. To date, more than 200 different diagnoses have been reported as possible causes of FUO but no single helpful algorithm could be developed [3]. According to Knockaert et al. [4], when no clues are found or when a clue does not point to the cause of the FUO, the subsequent approach may be: (a) a wait-and-see strategy, (b) a whole body inflammation tracer scintigraphy, (c) a staged approach, or (d) a therapeutic trial. In approaches b

and c, the ^{18}F-Fluorodesoxyglucose positron emission tomography ([18]FDG-PET) has the potential to play a central role as a second-line procedure [5,6]. Due to its high sensitivity for diagnosing infective, inflammatory, and neoplastic diseases, [18]FDG-PET is today considered among the first diagnostic tools for patients in whom conventional diagnostics have been unsuccessful [7].

A comparison between the most recent studies and historical surveys has revealed that:

- a high proportion of ''no diagnosis'' remains despite advances in serological, immunological, imaging, and genetic techniques;
- non-infectious inflammatory diseases (NIID) have replaced infectious diseases as the largest causes of FUO in Western countries [8].

A systematic review from 2003 forward has reported that 12 to 35% of hospitalized patients with FUO have died from FUO-related complications [9]. To the best of our knowledge few studies have recently addressed the clinical courses and mortality rates of FUO patients together with the roles of non-invasive tools, such as molecular biology, in the diagnosis.

We present here a series of nearly one hundred patients over a twelve-year period and describe their managements, diagnoses, and outcomes. We also evaluate the diagnostic role of [18]FDG-PET and bacterial or viral molecular biology assays.

Methods

Definitions and study design

From January 2002 to October 2012, we prospectively registered all patients who were seen at two departments of internal medicine of Lyon University Hospitals. These patients were referred by general practitioners or after an initial hospital assessment in other departments (e.g., infectious diseases or oncology).

Patients enrolled in this study were older than 18 years of age and fulfilled the criteria defined by Durack and Street [2]. These criteria are:

- a temperature exceeding 38.3 °C;
- duration of the fever of more than 3 weeks;
- evaluation of three outpatients visits or three days in hospital.

Learning points

- Half FUO cases are undiagnosed despite advances in serological, immunological, imaging and genetic techniques.
- Non-infectious inflammatory disorders emerge as the most frequent cause.
- Molecular biology techniques are useless when they are not directed by a hard clinical suspicion.
- The all-cause mortality rate among FUO patients is 10% and the FUO-related mortality among undiagnosed discharged patients is 4%.

Patients with history of immunosuppressive disease (e.g., HIV-positive), neutropenia (white-blood-cell count $< 1.0 \times 10^3/\mu$L and/or granulocyte count $< 0.5 \times 10^3/\mu$L), nosocomial infections, or with insufficient examinations were excluded (box 1). Episodic fever was defined as at least two episodes of fever with fever-free intervals of at least two weeks and apparent remission of the underlying illness [10].

According to the nature of the final diagnosis, the results of all tests performed were classified as contributory or not contributory. The study considered CRP values and treatments closest to the date of ^{18}FDG-PET. CRP was considered high when greater than 5 mg/L.

In accordance with the current French legislation, the ethical committee agreement is not a prerequisite for retrospective collection and analysis of observational data from clinical practice that does not change the routine management of patients.

^{18}FDG-PET

The final diagnosis was never based on ^{18}FDG-PET alone. As suggested in a meta-analysis by Dong et al. [7] and in a prospective study by Bleeker-Rovers et al. [11], the results of ^{18}FDG-PET were classified as:

- true positive (TP) when the pathological findings led to the direct determination of the correct diagnosis or when the recommended investigations resulted in a final diagnosis;

- false positive (FP) when the detected abnormality was considered to be unrelated to the illness causing fever or when no final diagnosis could be made;
- false negative (FN) when there were no suggestive foci and when a focal disease process was identified by another method and was considered to be the cause of FUO;
- true negative (TN) when no localized focus was found and when there was no evidence of disease after clinical follow-up. Here, the result of ^{18}FDG-PET was considered as contributory when it has guided a true-positive diagnosis and non-contributory otherwise. Non-contributory scans thus included all normal scans, all scans in patients without a final diagnosis, and abnormal scans in which the abnormality was judged irrelevant to final diagnosis or could not be further corroborated non-invasively (false-positive).

Molecular biology

Whenever bacterial or viral molecular biology methods were used, the sampling site was noted and the result was considered contributory when it allowed a positive diagnosis and non-contributory otherwise.

Final diagnosis

The causes of FUO were established during follow-up or at discharge and classified into five groups as proposed by Knockaert et al. [4]:
- infectious diseases;
- malignant diseases;
- NIID;
- miscellaneous causes;
- undiagnosed.

A diagnosis was considered as final when it was approved by all authors or when the patients fulfilled generally accepted criteria: i.e., the American College of Rheumatology criteria for giant-cell vasculitis [12], Fautrel's criteria for adult-onset Still's disease [13], and the American College of Rheumatology criteria for Henoch-Schönlein purpura [14].

A case was considered as undiagnosed when a final diagnosis could not be collectively approved.

Vital outcome

The vital status of all the patients was noted at end of follow-up or date of last contact. The monitoring of the cohort was conducted until December 2012. At this date, the vital status or the date of latest news was collected from the patients' medical records. Patients with unreliable vital status or latest news were considered as lost to follow-up.

Statistical analysis

Clinical and laboratory data were collected and analyzed by the same investigator (AR) using a standardized form approved by two other investigators (AR and PS). We used here only simple descriptive statistics.

Box 1
FUO patients' initial evaluation[1]

Biological analyses
  Complete blood count
  Erythrocyte sedimentation rate and C-reactive protein level
  Renal, and electrolytes
  Hepatic test
  Serum electrophoresis
  Serum levels of creatine phosphokinase, lactate dehydrogenase, and ferritin
  Beta-2-microglobulin test
  Antinuclear antibodies and rheumatoid factors tests
  Blood and urine cultures
  Serological test for viral hepatitis, cytomegalovirus, and HIV
  Tuberculin skin test
Imaging examinations
  Chest Radiography
  Abdominal & pelvic ultrasonography
  Abdominal & chest CT-scan.

[1] Not exhaustive for all patients.

A Robine, A Hot, D Maucort-Boulch, J Iwaz, C Broussolle, P Sève

Results

Patients and tests

The study included 103 patients who fulfilled the criteria for FUO. *Table I* shows the sex, age, and fever-type distributions; it shows also the numbers and percentages of patients who underwent specific laboratory tests.

Rheumatoid factors and antinuclear antibodies were never contributory to the final diagnosis. As a second step, anti-neutrophil cytoplasmic antibody (ANCA) helped establishing the diagnosis of microscopic-polyangiitis in two cases. Six patients did not have a thoracic-abdominal CT but a couple of chest X-rays and abdominal ultrasonography. The abnormal CT findings contributed to the diagnoses of nine cases: two cases of giant-cell arteritis with aortitis, two cases of micro-scopic-polyangiitis, and a single case of each of the following:

sarcoidosis, solid neoplasm, deep abscess, infectious polyseri-tis, and necrotizing lymphadenitis.

Diagnoses

Table II lists the diagnostic categories and the aetiology of the FUO in the 103 patients. In 52 cases, the aetiology could not be established.

TABLE I

Baseline variables

Characteristics and exams	n (%)	Mean	Median (range)
Age (yrs)		53.4	57 (19–84)
Male	54 (52)		
Continuous fever	65 (63)		
Recurrent fever	38 (37)		
Biological analyses			
Hemoglobin, g/dL	103 (100)	11.6	12 (6–16)
Leucocytes, 10^3/μL	103 (100)	9.5	8 (2–30)
C-reactive protein, mg/L	103 (100)	87.6	73 (1–300)
Serum electrophoresis	82 (80)		
Blood culture	103 (100)		
HIV serology	100 (97)		
Tuberculin skin test or QFT	71 (69)		
Antinuclear antibodies	90 (87)		
Rheumatoid factors	89 (86)		
Anti-neutrophil cytoplasmic antibody	66 (64)		
Imaging examinations			
Chest Radiography	82 (80)[1]		
Abdominal and pelvic ultrasonography	78 (76)[1]		
Abdominal and chest CT-scan	97 (94)		

CT: computed tomography; QFT: QuantiFeron tuberculosis.

[1] Patients had chest radiographies + abdominal and pelvic ultrasonography.

TABLE II

Final diagnoses

Final diagnosis	n (%)
None	52
Infections	12 (23.5)
Deep abscess	1
Bacteriemia	1
Endocarditis with negative blood cultures	2
Bone and joint infections	1
Atypical mycobacteria	1
Polyseritis	1
Extra-pulmonary tuberculosis	1
Cytomegalovirus	4
Non-infectious inflammatory diseases	31 (60.8)
Dermatomyositis	2
Rosai-Dorfman disease	1
Behcet's disease	1
Giant-cell arteritis	13
Adult-onset Still's disease	6
Micropolyangiitis	2
Schönlein-Henoch purpura	1
Remitting seronegative symmetrical synovitis	1
Sarcoidosis	2
Schnitzler syndrome	1
Hyper-IgD syndrome	1
Tumors	3 (5.9)
Non-Hodgkin lymphoma	1
Solid tumors	2
Miscellaneous	5 (9.8)
Drug fever	2
Familial Mediterranean fever	1
Necrotizing lymphadenitis	1
Hemophagocytic syndrome	1

Among the 51 patients with final diagnosis, NIID was the most frequent cause of FUO (31 cases). Giant-cell arteritis and adult-onset Still's disease were the most common etiologies in this category (13 and 6 cases, respectively). Thirty one temporal artery biopsies were performed in 31 patients; among the 3 patients over 50 and 60 years who underwent this procedure, one had biopsy-proven giant cell arteritis. Serum ferritin was measured in 99 patients and found increased in 38 patients, including all adult-onset Still disease. Glycosylated was measured at diagnosis in three of these later and found ≤ 20% of serum ferritin in 2 of them. In twelve cases, the fever was of infectious origin. Miscellaneous causes grouped nearly 10% of the diagnoses of which the most frequently was drug fever. Malignancies were diagnosed in three patients.

18FDG-PET results

18FDG-PET was used in 48 patients. The use of the method did not increase over the study period; 24 scans between 2002 and 2006 and 24 scans between 2006 and 2012. 18FDG-PET was considered contributory (i.e., led to true-positive diagnoses) in ten patients. The 18FDG-PET-established diagnoses were six NIID (giant cell arteritis [4 cases], sarcoidosis [2 cases]), one lymphoma, one solid tumor, one Rosai-Dorfman disease, and one Kikuchi-Fujimoto disease. In the patients who had no final diagnoses, abnormal 18FDG-PET results were considered as false-positive in 19 patients and normal 18FDG-PET results were considered as true-negatives in 19 other patients. Seven (36.8%) of abnormal and useless PET scans were followed by further explorations, sometimes invasive but never complicated. Among the patients who underwent 18FDG-PET, 28 patients did not have final diagnoses at discharge (table III). There were no significant correlations between the 18FDG-PET and CRP or WBC values. All but one patient underwent a CT examination within three months after 18FDG-PET; this patient

TABLE III

Results and contribution of 18FDG-PET to the diagnosis

Diagnosis	Normal 18FDG-PET	Abnormal 18FDG-PET	
		Contributive	Non-contributive
NIID	1	7	7
Infections	3	0	0
Neoplasms	0	2	0
Miscellaneous	0	1	0
No diagnosis	15	0	12
Total	19	10	19

NIID: non-infectious inflammatory disease.

underwent a chest X-ray (found normal) and an abdominal ultrasonography (found abnormal but not contributory). Chest and abdomen CTs pointed to abnormalities linked to the final diagnosis in only six of the patients who underwent 18FDG-PET. 18FDG-PET was not contributory in two of these six patients with abnormal CTs (one case of deep abscess and one case of giant-cell arteritis with aortitis under corticosteroid therapy at the time of the 18FDG-PET).

Six patients with non-contributory chest and abdomen CTs had a true-positive 18FDG-PET. The final diagnoses of these patients were: giant-cell arteritis (three cases), non-Hodgkin lymphoma (one case), sarcoidosis (one case), and Rosai-Dorfman disease (one case). The CRP level of these six patients was significantly lower than that of the patients with abnormal CTs that guided diagnosis (mean, median, and range values: 59.6, 32.5, and 23–135 mg/L versus 161.8, 183, and 12–269 mg/L). In these patients, the other characteristics did not differ significantly.

Molecular biology results

Molecular biology techniques were used in 28 patients in a total of 41 tests. The most frequent was *Tropheryma whipplei* PCR (14 patients: duodenal biopsy [5 samples], blood [9 samples], node biopsy [2 samples], bone marrow, cerebrospinal fluid and aqueous humor [one sample each], no positive results), Cytomegalovirus PCR (11 tests, 2 positive results, of which only one was finally considered as cause of the FUO), bacterial 16S rDNAPCR (5 patients: blood [3 samples], node biopsy [3 samples], cerebrospinal fluid and aqueous humor [one sample each], no positive results), *Bartonella* PCR (4 patients: blood and node biopsy [3 samples each], no positive results), and Mycobacterium tuberculosis PCR (3 patients: blood [one sample] and node biopsy [2 samples], no positive results). Other tests were used only once: Leishmania PCR, Borrelia PCR, Parvovirus B19 PCR, and HHV6 PCR.

Three-month follow-up outcomes

Twenty-three patients were followed for 3 months or less. Over this period, one of them died from an unexplained hemophagocytic syndrome and another from severe pulmonary interstitial fibrosis (after microscopic polyangiitis). Among the other 21, 10 remained without final diagnosis but their condition did not require further evaluation or treatment. The eleven diagnoses established during this short period were: infectious disease (four cases), NIID (four cases), neoplasm (two cases), and drug fever (one case).

Vital outcomes

During entire follow-up (mean duration: 28 months), eleven patients out of the 103 died. The mean time to death was 29 months (table IV).
Death was considered unrelated to the febrile illness in six patients. One patient died from myocardial infarction 107

Vital outcomes over whole follow-up

Vital status	n (%)	Median (min–max)[1]
Alive at last contact	92 (89)	19 (1–108)
Deaths during whole follow-up	11 (11)	15 (1–107)
Unrelated to the febrile illness	6 (5.8)	27.5 (15–107)
No final diagnosis	2 (2)	19 (15–23)
Related to the febrile illness	5 (4.9)	4 (1–6)
No final diagnosis	2 (2)	5.5 (5–6)

[1] In months.

months after a diagnosis of Schnitzler syndrome. The second patient died also from myocardial infarction 15 months after a transitory and diagnosed fever episode. The third patient died from a chronic renal failure 104 months after diagnosis of an adult-onset Still's disease. The fourth patients died from breast cancer 23 months after admission while fever had stopped and remained of unknown origin. In the two remaining cases the cause of death was not found and the cause of fever remained undiagnosed.

Death was considered related to the febrile illness in five patients: three with diagnosis (hemophagocytic syndrome, microscopic polyangiitis, tumor), and two without diagnosis (43 and 44 years old). The latter patient died less than six months after admission due to the seriousness of their condition. Their mean delay to death was 3.8 months.

Treatment outcomes

At end of follow-up, 20 patients without final diagnosis were considered cured. Two of them had received a cyclin treatment without demonstrated efficacy. Seven patients are still followed-up (median duration: 38 months; range: 7–96 months): three are currently untreated, two are receiving colchicin, one is receiving NSAIDs, and the other methotrexate and corticosteroids.

Twenty other patients with unreliable latest news at end of follow-up were considered as lost to follow-up.

Discussion

In this retrospective study of 103 cases of FUO, we provide insights about the use of techniques such as [18]FDG-PET or molecular biology in the diagnostic strategy.

Diagnoses

Our study confirms the high percentage of patients without diagnosis at the end of the investigations reported in recent studies [6,11]. Here, half the cases remained undiagnosed, which is in agreement with the results of a prospective multicentric study by Bleeker-Rovers et al. [15] and those of a prospective monocentric study by Buysschaert et al. [6] who reported 53% and 47%, respectively. Though insufficient, the diagnosis of one case out of two may be due to the easier and earlier use of specialized exploration tools, such as high performance CT. At the same time, patients and physicians promptly perform specialized consultations and paraclinical examinations. Another explanation suggested by Bleeker-Rovers et al. [15] is the diagnostic strictness that others and we have applied. [6,11,15]. Diagnoses lacking persuasive confirmatory tests were accepted only if sufficient standard criteria were met and follow-up allowed exclusion of other diseases. On the other hand, Vanderschueren et al. [9] noted that patients without diagnosis are kept in relatively good health and undergo less aggressive treatments. The final diagnoses did not differ significantly from those found in the most recent studies carried out in Northwestern Europe or the United States [6,8,15]. NIID was the most frequent (29%) followed by infectious diseases (12%) then miscellaneous causes (6%). The same trend was reported by other studies in populations with similar characteristics [8,9,15]; however, here, the proportion of NIID is higher. This may be explained by the fact that the present study was conducted in internal medicine departments and that one of these was close to an infectious disease department. In addition, the proportion of temporal arteritis was also important (13 cases) and most cases were proven by a positive temporal artery biopsy (8/13). In another French retrospective study, Zenone [8] reported a similar rate. Nevertheless, the decrease of the rate of infectious diseases is constant. The difference with studies from Southern Europe [16–18] may be due to the high incidence of tuberculosis.

To face the diagnostic challenge of FUO, many test and tools have been assessed: whole-body CT-scan, echocardiogram, bone marrow biopsy, temporal artery biopsy, etc. [3,4,19,20]. Because ^{18}F-FDG accumulates in neoplastic cells and in non-neoplastic conditions such as infectious diseases, sarcoidosis, and large vessel vasculitis, [18]FDG-PET has been extensively used for the diagnosis of FUO [21]. According to a review by Balink et al. [21] on 15 studies, the percentage of contributory [18]FDG-PET scans varied between 16 and 77%. Comparing these 15 studies is difficult because of the heterogeneity of the patient populations, the wide range of possible causes of FUO, and the differences in inclusion criteria and PET techniques [7,11,22–24].

[18]FDG-PET

[18]FDG-PET appears to have a very low negative predictive value in ruling out miscellaneous causes of FUO that cannot be reliably visualized by conventional techniques. The rate of our contributory [18]FDG-PET examinations was moderate (21%) but allowed finding a diagnosis in six cases in which conventional CT was not contributory. The relatively low number of positive

18FDG-PET may be due the low frequency of infections and cancers and the high frequency of NIID and unknown diagnoses. Several studies reported that 18FDG-PET sensitivity was highest in case of tumors or infectious diseases than in autoimmune or connective tissue diseases [25] and that the high prevalence of infectious diseases in non-university hospitals may affect the effectiveness of 18FDG-PET in diagnosing FUO. One case of deep abscess and one case of giant-cell arteritis with contributory CT had a non-contributory 18FDG-PET; this highlights the importance of conventional CT since the advent of a new generation of high-resolution equipment. Nevertheless, the moment of conventional CT use is still widely debated: before 18FDG-PET for some authors [26] vs. after non-contributory 18FDG-PET for others [11]. Our results highlight the place of 18FDG-PET in the diagnosis of difficult FUO cases. We suggest that, given the increasing availability of conventional CT, this examination should be carried out first in replacement of the couple chest radiography + abdominal ultrasonography and that 18FDG-PET would find a better place in second-step tests but, for the most profitable results, should be used early in case of non-contributory CT.

Like other authors [25], we did not find predictors of high-yield 18FDG-PET. A French retrospective study from a department of infectious diseases has shown that the presence of lymphadenopathy, low hemoglobin, or increased CRP was predictive of contributory 18FDG-PET [24]. Bleeker-Rovers et al. [11] showed that 18FDG-PET was significantly more often contributory in patients with continuous fever and never contributory in patients with normal erythrocyte sedimentation rate and CRP. Overall, these studies have shown that 18FDG-PET is a sensitive technique for the evaluation of FUO. However, a large multicentric study using 18FDG-PET as part of a structured evaluation protocol is needed to determine its diagnostic value and level of evidence.

Molecular biology

To our knowledge, only one study has assessed the yield of CMV and tuberculosis PCR blood tests in diagnosing FUO [27]. In Mete's study on 100 patients with FUO, CMV and tuberculosis PCR were performed in 4 and 27 patients, respectively, and positive results were obtained in 16% (four tuberculosis and one cytomegalovirus infection) [27]. In the present study, a positive PCR result for CMV was obtained in one patient with a positive serology, but other PCR were not contributory for detecting microorganisms regardless of the sample origin. As previously described in microbiologic serology [28], the diagnostic yield of molecular biology, except for CMV detection, appears to be very low on blood samples; thus, such investigations should not be used as screening procedures early in the diagnostic process in patients without diagnostic clues. Furthermore, a diagnostic protocol with routine serology should be adapted to the local epidemiological conditions; i.e., serology for *Brucella*, *Leishmania*, and *Coxiella burnetii* in high incidence areas [3].

Vital outcomes

Little is known about the mortality rates in patients with FUO. In 1996, Knockaert et al. reported a 10% mortality rate among 61 patients followed-up for five years without FUO diagnosis [29]. At end of follow-up, four were considered to be cured but two died from fever-related complications. In 1997, De Kleijn et al. described 167 patients with FUO of whom 20 (12%) died during follow-up, including 18 with established diagnosis [28]. In 2003, Vanderschueren et al. reported the outcome of a series of 290 FUO patients referred to a university hospital [9]. Sixteen patients died during the index admission and 18 during the follow-up leading to a mortality rate of 20% (41 lost to follow-up). Hematological malignancies made up 11.5% of the diagnoses but were responsible for 14 of the 24 deaths related to the febrile illness. Of the 80 patients discharged alive without diagnosis, 3 died later from causes unrelated to the feverish illness. Zenone et al. reported one fever-related death (2.7%) among 37 undiagnosed FUO patients [8]. We report here a global mortality rate of 11% and a fever-related death rate of 4.9% (five patients). Of the 52 cases without final diagnosis, five patients (10%) died during follow-up of which two early deaths were attributed to the febrile illness.

Generally, the all-cause mortality rate among FUO patients is still 10% or greater. Despite advances in diagnostic tools and techniques, early FUO-related deaths occur in a small proportion of patients. Our study also shows that the absence of final diagnosis at end of follow-up is not an element of worse prognosis.

Limitation

Although the present study provides additional information on the diagnosis and prognostic features of FUO, it has a number of limitations. First, the study was retrospective, non-comparative, and had to deal with missing clinical or laboratory data. Besides, its retrospective nature generated difficulties in patient recruitment because there is no specific code for FUO in the local discharge abstracts; it is the final diagnosis that is often reported. A prospective study would have provided much clearer and exhaustive data and permitted a much larger patient recruitment.

Another limitation is that the study was carried out in two departments of internal medicine at a single university hospital and might have included a higher percentage of non-infectious inflammatory diseases than what would be expected in a primary setting. Thus, the present results are generalizable only to secondary or tertiary internal medicine departments. Moreover, the spectrum of diseases and management strategies differ widely between countries, hospitals, and even physicians. Therefore, additional studies by other institutions

in various countries are awaited to complement the present results.

Conclusions

The management of FUO remains a difficult challenge. The long list of more than 200 disorders encompasses not only rare diseases but also a high number of common diseases that remain long undiagnosed because of atypical presentations. The present study confirms:
- the high percentage of patients without final diagnosis;
- the progressive replacement of the infectious category by the NIID category as the largest cause in Western countries;

- the constant rates of the overall mortality among FUO patients (nearly 10%);
- the FUO-related mortality among undiagnosed discharged patients (nearly 3%).

The diagnostic role of [18]FDG-PET seems interesting but its exact place in the staged strategy is not clear yet; it varies according to the characteristics of the patient population and the inclusion criteria. Its use early in the diagnostic process seems to be helpful but its rank relative to conventional CT is still uncertain.

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