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Classical fever of unknown origin (FUO): current causes in Mexico

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ABSTRACT

Background. Causes of FUO change according to medical innovations, modifications of social circumstances, and emerging health risks. **Aim.** To describe the epidemiology of classical FUO, the time and procedures to achieve a definitive diagnosis, and to underline the variables useful in distinguishing FUO categories. **Setting.** A third-referral center in Mexico City. **Methods.** Patients admitted with prolonged fever were evaluated. Clinical charts of patients with classical FUO were assessed; comparisons between classical FUO categories were made. **Results.** 45 patients with 44.9 ± 17.2 years of age, previous fever duration of 51.2 ± 51.5 days, and 88.9% referred from other hospitals were evaluated. Nineteen patients had infectious causes; eight, neoplastic conditions; 12, inflammatory non-infectious diseases; one had another cause, and five were discharged with no etiologic diagnosis. Age, LDH levels, length of fever, and weight loss greater than 10 kg may be used to classify patients into a definite category. **Conclusions.** Classical FUO is an unusual presentation of frequent infectious diseases; SLE is the main cause within the inflammatory non-infectious conditions, and non-Hodgkin's lymphoma is the first cause of cancer. Some clinical and laboratory clues may be used to guide the study work up of patients with classical FUO.

Key words. Epidemiology. Third-referral center. Mexico. Viral infection. Systemic lupus erythematosus.

Fiebre de origen indeterminado (FOI): causas actuales en México

RESUMEN

Las causas de fiebre de origen indeterminado (FOI) varían de acuerdo con las innovaciones médicas o con modificaciones de las circunstancias sociales y riesgos para la salud. ***Objetivo.*** *Describir la epidemiología de la FOI, el tiempo y procedimientos empleados para alcanzar un diagnóstico definitivo y evaluar las variables que pueden usarse para diferenciar sus categorías.* ***Hospital.*** *Centro de referencia de tercer nivel de la ciudad de México.* ***Métodos.*** *Se evaluó a pacientes con fiebre prolongada; los expedientes clínicos de aquellos con FOI fueron analizados y se compararon sus principales categorías.* ***Resultados.*** *Fueron evaluados 45 pacientes, de 44 ± 17.2 años de edad y duración promedio de la fiebre de 51.2 ± 51.5 días, de los cuales 88.9% habían sido referidos de otros hospitales. De ellos, 19 fueron diagnosticados con causas infecciosas, ocho con enfermedades neoplásicas, l2 con enfermedades inflamatorias no infecciosas, uno por alguna otra causa y cinco fueron dados de alta sin diagnóstico definitivo. La edad, niveles de DHL, la duración de la fiebre y la pérdida de peso mayor de 10 kg fueron marcadores útiles para clasificar a los pacientes en alguna de las categorías de la FOI.* ***Conclusiones.*** *La FOI es una manifestación inusual de enfermedades infecciosas frecuentes, el lupus eritematoso generalizado es la causa principal dentro de las condiciones inflamatorias no infecciosas y el linfoma no-Hodgkin en las neoplásicas. Algunas pistas clínicas y de laboratorio pueden emplearse para guiar el estudio de pacientes con FOI clásica.*

Palabras clave. *Epidemiología. Tercer nivel de referencia. México. Infección viral. Lupus eritematoso sistémico.*

INTRODUCTION

After 40 years of the original description of FUO,[1] it remains as one of the most important challenges for clinicians. FUO is a changing field that requires of frequent updating according to the variation of its causes and factors such as the widespread and early use of more powerful antibiotics and more accurate image studies, plus the availability of more precise laboratory studies, which may preclude the progression of the formerly frequent infectious causes of FUO[2]. On the other hand, the epidemiology of the population is also changing, with a longer life expectancy, and larger number of patients with immune system compromise that necessarily implicate more patients at risk for febrile conditions. Finally, the characteristics of each hospital and its area of reference also influence FUO etiology, with geographical and regional variations among them.[3,4]

In Mexico, series of adult patients with FUO have been reported by only one third-referral center.[5-7] Its epidemiology has been updated approximately every decade since the 60's. Reports on this matter showed a progressive reduction of the infectious causes, and a rise in systemic autoimmune diseases and neoplastic conditions; meanwhile the average of undiagnosed cases remained stable.

Furthermore, the FUO criteria have evolved since its very first descriptions, mainly because patients' studies are performed more frequently on an outpatient basis, and methods to diagnose infections, even with molecular biology techniques, are widely available; invasive and sophisticated image studies are used earlier, and clinicians have a more efficient and systematic clinical approach. At the present time, FUO is divided into four different categories: classical FUO, nosocomial FUO, FUO of immune-compromised patient, and HIV-associated FUO. Hence, the time required for the fulfillment of the diagnostic criteria, from the begining of the study to the achievement of an etiologic diagnosis, and the length of hospitalization, have also been shortened.[8]

We decided to evaluate the causes of classical FUO in a third-referral center in Mexico City, assess the accuracy of the final diagnosis, and evaluate if some parameters can be qualified as relevant in the study of these patients, thus contributing to improve the diagnostic performance.

METHODS

The Hospital

Our Hospital is the third-referral Center of our Medical System; it is also the national reference center for malignant hematological diseases, and "difficult" cases, including patients with systemic autoimmune diseases or chronic infections. The Hospital has 120 bed for adults and admits patients from Mexico City (30% of hospital admissions); southeastern Mexico (60% of admissions from the states of Morelos, Guerrero, Oaxaca, Veracruz, Puebla, Tabasco, Chiapas and Campeche), with the complementary 10% coming from the rest of the country. Patients referred from other hospitals do not require any special condition to be sent; they are admitted with a simple request by their treating physicians. Indeed, referral is ultimately based on the physicians' judgment; however, patients with medical conditions in whom a final diagnosis has not been achieved, or those considered with prolonged hospitalization are sent, again, without any reference filter. Available image resources are last-generation ultrasound, color-ultrasound, and color Doppler, last-generation tomography, as well as complete laboratory tests including protein chain reaction and other molecular biology techniques. Scintigraphy and IMR studies are available upon request. Practically all studies are on hand promptly (at most, 72 working-hours after referral) looking after in-hospital cost reduction. Furthermore, once a patient is admitted with diagnosis of fever, an infectologist, a rheumatologist and a hematologist, as well as three different general internists, evaluate the case.

In our Hospital, febrile illnesses are initially studied under clinical basis; those with longer febrile episodes or with no evident clinical features have blood, urine and stool cultures performed. Vitek-2 system was used for rapid bacterial identification, and antimicrobial susceptibility; standard culture media were used in all cases. Special culture techniques, such as duplicate cultures, were requested when suitable clinical and epidemiological circumstances were present.

FUO criteria

For the purposes of this study, all cases included completed the Petersdorf-Besson[1] criteria modified by Durack-Street[8] that contain the following items.

1. Fever (body temperature of 38.2°C or higher) for at least two weeks, with no evident diagnosis despite the completion of all "primary studies" (Table 1). Additionally, any of the following events:
2. At least three ambulatory visits at our external consultation area conducted by a physician of our team, where "primary studies" had been completed with no conclusive diagnosis, or

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Table 1. "Primary studies" used in this study.

- Comprehensive clinical history
- Physical examination performed in an ex professo assessment by a clinical team
- Complete blood cytology with manual evaluation of WBC
- Clinical chemistry including: glucose, BUN, creatinine, uric acid, AST, ALT, total proteins, albumin, total cholesterol, triglycerides, LDH, AST, ALT, alkaline phosphatase, amylase, total and conjugated bilirrubin
- Urinalysis with manual evaluation of sediment
- Erythrosedimentation rate
- Febrile agglutinins
- Viral studies for hepatitis (A, B and C)
- C-reactive protein
- Three blood cultures in a febrile episode, and urine culture
- Febrile agglutinins
- Stool, throat and bone marrow cultures when clinically indicated
- Antibodies against VIH-1 & 2; cytomegalovirus, and toxoplasma
- Chest and abdominal X-ray
- Pelvic, renal, and gallbladder ultrasound
- Double-contrast chest and abdominal scan tomography
- Bone marrow culture and smear assessment

3. Three days hospitalization in our department after at least two previous weeks with fever and no diagnosis, or
4. One week of "intelligent" study work up in another hospital, after three previous weeks of fever ("primary" studies were completed there or accomplished in the first three days in our Hospital).

Patients

All cases hospitalized in the Internal Medicine Department between January 1996 and May 2002 were selected from the admission and discharge archives; Central Hospital registry and database with the ICD-10 numbers R50.0, R50.1 and R50.9, as well as the codes A68.X, A68.9, R59.X and R59.9 were selected. For inclusion in the analysis, it was required that clinical charts had complete and explicit information about the out and in-hospital clinical assessment and diagnostic procedures. HIV-seropositive patients and those with a known diagnosis of an autoimmune or neoplastic condition were excluded in order to evaluate only cases with classical FUO.

Variables

Variables evaluated were clustered in the following groups:

1. Epidemiological characteristics such as age, relevant past history, toxic substances exposure, alcohol or drugs consumption; recent (no more than six months apart) surgeries, trauma or travels; close contact with animals; and hazardous sexual practices;
2. Related with fever: pattern of presentation, symptoms associated with fever, number of visits as outpatient, previous studies, previous hospitalizations related to fever, and former therapeutic interventions, i.e.: medical or surgical;
3. Clinical characteristics at admission, with emphasis on adenopathy, visceral enlargement, and features on muscular, neurological and joint examination; two different observers had to report eye fundoscopy and skin evaluation. During the first three days in our Hospital, the "primary studies" had to be accomplished; further studies were guided by the clinical data or the "primary studies" results. Moreover, length of hospitalization, clinical condition at discharge and therapeutic interventions during hospitalization at our center were also registered.

Analysis

We used descriptive statistics for the presentation of data, mean and standard deviations are described, and when indicated, median is used. Fisher's exact test was used for the comparison of proportions whereas for the comparison of continuous variables, the Mann-Whithey U-test was utilized given the skewed distribution of groups. Logistic regression was used for the significant variables in the univariate comparisons within the FUO categories. Significance was considered when $p < 0.05$, and all were two tail comparisons.

RESULTS

From 1996 to 2002, we found 91 patients with prolonged (more than 10 days) and unexplained fever as the initial hospitalization diagnosis. Thirty-five of these cases did not comply with the classical FUO criteria; in addition, five patients were rejected because they belonged to other FUO categories (two known HIV-seropositivity, two with previous diagnosis of leukemia, and one with a known necrotizing vasculitis), and six because not enough information on them was available. Finally, 45 patients met the inclusion criteria; 18 were women, 27 men; the mean age of the group was 44.9 ± 17.2 years. The most relevant data of this group is described in table 2. Importantly, nearly 90%

Table 2. Relevant patient data at admission.

Item	
Gender; n (%) / M:F	27 (60) : 18 (40)
Age; years / μ ± SD [range]	44.9 ± 17.2 [16-74]
With diabetes; n (%) / yes: no	14 (31.8) : 30 (68.2)
With surgical procedures in the last six months; n (%) /yes: no	11 (24.4) : 34 (75.6)
With blood transfusion in the last six months; n (%) /yes: no	8 (17.7) : 37 (82.2)
Referred from other hospital; n (%) /yes: no	40 (88.9) : 5 (11.1)
Previous hospitalization due to fever; n (%) / yes: no	39 (86.7) : 6 (13.3)
Length of fever prior to admission in our Hospital; days / μ ± SD [range]	51.2 ± 51.5 [14-270]
Length of persistence with fever in our Hospital; days / μ ± SD [range]	17.7 ± 19.1 [2-80]
Duration in our hospital until definitive diagnosis; days / μ ± SD [range]	18.2 ± 10.6 [6-57]
Weight loss >10 kg; n (%)	22 (48.9)
Previous empiric treatment; n (%) antibiotics/anti-TB/steroids	33 (73.3) /9 (20) /3 (6.7)

Table 3. Comparison of variables between classical FUO categories.

	Infectious diseases n=19 [††]	Inflammatory non – infectious diseases; n=12	Malignancy; n= 8
With skin or mucosal alterations;* n (%) [†]	1 (5)	7 (58)	2 (25)
With musculoskeletal anomalies;* n (%)[‡]	8 (40)	12 (100)	4 (50)
With > 10 kg of weight loss;* n (%)	7 (36)	8 (66)	6 (75)
Age, years;[§] median (range)[‖]	38 (17-67)	44 (16-74)	61.5 (30-73)
AST level, IU/L;[§] median (range) [‖‡]	50 (30-380)	42.5 (16-122)	88.5 (47-365)
ALT level, IU/L[§] median (range)[†]	40 (30-185)	37.7 (25-108)	62.5 (35-140)
LDH level, IU/L[§] median (range) [‡‖†]	350 (200-580)	250 (123-469)	581 (250-1593)
Alkaline phosphatase, IU/L[§] median (range) [†]	150 (90-306)	126 (55-355)	129.5 (110-350)
ESR, mm/h;[§] median (range)[†‖]	46.5 (15-69)	47 (12-63)	57 (49-71)
Fibrinogen, mg/dl;[§] median (range)[‖]	473 (200-993)	649 (311-900)	746 (490-790)
Fever duration, days;[§] median (range)	37 (20-195)	59.5 (27-211)	116 (27-278)

* Fisher's exact test. [§] Mann-Whitney U-test. [†] p < 0.05 for the comparison of infectious against inflammatory non-infectious diseases. [‖] p < 0.05 for the comparison of infectious against cancer patients. [‡] p < 0.05 between inflammatory non-infectious diseases and cancer. [††] Number of patients per group.

of these patients were referred from other second-level hospital where they underwent a non-systematic evaluation of fever, with inconclusive results. Even though 25 of these patients had no definite diagnosis (nine cases sent without any clinical suspicion, 16 sent with FUO diagnosis, and the remaining cases had only a syndromatic diagnosis), practically all patients included in the final analysis received previous treatment: antibiotics in 33 cases, antituberculosis medication in nine cases, systemic steroids in three, and two cases with no treatment. Most were short-lived courses of treatment.

Weight loss was absent in nine patients, loss of 1-5 kg in nine patients, between 5 and 10 kg in five cases, and larger that 10 kg in 22 subjects.

On the other side, despite the fact that some studies had yielded positive results in their previous hospitalization, these were not consistent with the final cause of fever, and febrile episodes did not improve with specific treatments. There were two cases that had positive serologic studies in their respective hospital, one for *Brucella* and other for *Salmonella*, but they did not respond to antibiotics, and were eventually sent to our Hospital; final diagnoses in these cases were not of an infectious nature. Six patients underwent surgical procedures as a part of the diagnostic evaluation of fever in their referral hospital, five biopsies (four lymph nodes and one of skin), and one had an exploratory laparotomy, all with inconclusive results.

Once admitted to our Hospital, patients were thoroughly reviewed in search of mild clinical alterations that could guide the initial studies. The most common abnormalities were: pleural effusion or pulmonary rales in 25% of cases; cardiac murmurs or tachycardia in 20% of patients; lymph node enlargement, hepatomegaly or palpable spleen in 40%, diarrhea in other 20%. Skin or mucosal abnor-

malities, such as facial rash, hair loss or oral ulcers, detected in 25% of cases; while joint tenderness or muscular weakness was observed in 20% of cases.

Accordingly to the main causes of classical FUO, 19 patients were diagnosed with infectious causes; in 12 an inflammatory non-infectious condition was demonstrated, and eight had diagnosis of cancer. Comparisons of the main variables between the final diagnostic groups are shown in table 3. Patients with infectious diseases were younger than patients in the other groups. In regard to clinical manifestations, those with mucosal or cutaneous lesions, i.e.: cutaneous erythema, oral ulcers or diffuse hair loss, were most likely to be diagnosed with a non-infectious inflammatory condition (p = 0.002, compared with the group of infections). Furthermore, cases with small joint arthritis, knee arthritis, or muscle weakness were more often found in non-infectious inflammatory conditions compared with the infectious group. Moreover, in relation to laboratory studies, for patients with cancer, LDH levels were the highest and statistically different when compared with both infectious and inflammatory non-infectious groups; LDH levels were also higher in patients with infectious disease compared with inflammatory conditions. Meanwhile serum levels of AST, and non-corrected ESR at admission, were significantly higher for cancer patients when compared with those who had an inflammatory non-infectious disease. Involuntary weight loss, more than 10 kg, occurred in 66% of patients with inflammatory non-infectious disease, 75% of cancer patients; and only 36% of patients with infectious conditions. Nevertheless, this feature was not statistically different among the groups.

The median of day-stay in our Hospital, since admission until the achievement of an etiologic diagnosis of fever was 16 days (range 6 to 57 days); less time than the average of the former hospitalization (Table 2). Five patients were discharged after five consecutive days without fever, but with no definitive diagnosis; two of them were readmitted, one patient was diagnosed with Q-fever, and the other with non-Hodgkin's lymphoma during the first week of their second hospitalization. Patients in the group of infectious causes had the shortest length of hospitalization until the achievement of a definitive diagnosis (median of 13.5 days); the inflammatory non-infectious group had a median of 16.5 days, and the cancer group stayed a median of 19 days. One case extended his hospitalization beyond 50 days; after that time, fever disappeared, and he was discharged without definitive diagnosis; however, fever did not recur in the next twelve months.

In logistic regression comparison between infectious and neoplastic groups' differences were sustained for the presence of weight loss larger than 10 kg in the neoplastic group OR 7.14 (95% CI = 1.2 to 42.1), and higher levels of DHL OR 1.2 (95% IC = 1.05 to 1.35). For the comparison between inflammatory non-infectious diseases and infectious disease, patients in the later group were younger, OR 0.9 (95% CI = 0.83 to 0.98), and had lower levels of LDH, OR 0.95 (95% CI 0.9 to 0.98)

Infectious conditions

As in previously reported series (Table 4), infectious diseases remain as the main cause of classic FUO. Nevertheless, and perhaps due to the effectiveness of current diagnostic approach, previous frequent causes, such as tuberculosis, occult abscesses or salmonellosis represented only few cases with infectious diseases in our series, whereas viral infections represented 35% of these cases, predominantly HIV acute infection. Bacterial endocarditis and brucellosis had two cases of each disease.

Table 4. Percentage of the main reported causes of classical FUO.

Author[Ref]	Infections	Malignancy	Inflammatory non – infectious condition	Other causes	No. diagnosis
Petersdorf[1]	36	19	15	23	7
Sheon[16]	21	6	13	20	40
Lascuráin[6]	40	27	27	-	6
Larson[11]	30	31	19	8	5
Knockaert[12]	22.5	31	21.5	8	17
Molina-Gamboa[7]	40	23	21	6	16
De Kleijn[17]	25.7	12.6	40	-	29.9
This study/2004	42	18	26	2.5	11.5

Non-infectious inflammatory disease

In previous series, some illnesses are classified as "rheumatic" or "autoimmune" conditions, and some others are included in the chapter of miscellaneous diseases, but clearly different from infections and cancer. As De Kleijn,[9] we prefer to cluster these maladies in one category, namely non-infectious inflammatory diseases, which encompass autoimmune systemic illnesses (connective tissue diseases, and vasculitic disorders), and other chronic inflammatory diseases, sarcoidosis, vasculitic syndromes, and chronic non-infectious granulomatous diseases. These conditions were the second most frequent cause of classical FUO in our series, being system-ic lupus erythematosus 50% of all cases, and polyarteritis nodosa, 25%. Dermatomyositis, Crohn's disease and other forms of vasculitis were also represented.

Cancer

This group was, in order of incidence, the third cause of classical FUO in our series, strikingly low-er than the frequency of other series. Non-Hodgkin's lymphoma was diagnosed in 75% of these cases. In two of these, diagnosis was reached through a bone marrow smear, suggesting infiltration by neoplastic lymphocytes; then patients underwent further orien-ted evaluation. Another case, whose important featu-re was pancytopenia, received the diagnosis of mye-loptisis associated with an adenocarcinoma of unknown primary localization; patient denied fur-ther interventions and was discharged with palliati-ve measures.

Other FUO causes

One elderly patient was found with a large thorac-ic and abdominal aortic aneurysm with no other re-lated possible causes of persistent fever; he denied offered surgical procedure and was discharged with antipyretic therapy.

No final diagnosis

Five cases had no definitive etiologic diagnosis of fever despite a systematic and extensive review; one had the largest hospitalization in our series. Howev-er, in all of these, fever disappeared during hospital-ization, and did not recur in the follow-up wich last-ed three years. Likewise, no other clinical or laboratorial abnormalities were found in this time span.

DISCUSSION

Classical FUO usually represents, accordingly to diverse authors,[10-13] a rare manifestation of a com-mon disease. Moreover, its causes, methods imple-mented to achieve a definitive diagnosis, and the time required to study this condition, have been changing in the last decades.[8] Nonetheless, this syn-drome remains a challenge for clinicians.[2] In Mexico, reported experience is limited to one group.[5-7] Con-cerns about over-selection of cases, in these previous work, have been raised. Furthermore, clinical re-sources vary and there are also geographical varia-tions that need to be explored.[3,4,14,15]

Current trend is to study febrile patients on an outpatient basis and try to save costly diagnostic in-terventions. Yet this aim might not be entirely applicable in less-affluent communities where first-contact physicians do not have all the needed diag-nostic tools[16] and patients are frequently hospitalized for longer periods of time. In this series, it would ap-pear worrying that in spite of, the technological ad-vances that benefit the second-level hospitals in our medical system (for example: advanced laboratory, radiological, and histological resources) 90% of pre-viously studied patients were sent to our Hospital with indeterminate results. One possible explanation for this failure might be that some diseases require longer times to be recognized. However, this may also have to do with the tendency of physicians to underestimate clinical data (wich may be recognized early in the course of the disease) in favor of "hard-er" non-clinical features, considered more reliable, but certainly confounding. Clinical assessment maintains its diagnostic accuracy, and exerts a nota-ble contribution in reaching a definitive diagnosis, particularly in those cases with a non-infectious in-flammatory condition (shown in Table 3), since most patients in this group had muscle-skeletal and skin features. Without disbelief, FUO cases demand the most complex model of medical attention and cooper-ation among different subspecialties.

Definitive diagnoses found in this series remain in the same proportion of other previously reported pa-pers,[1,9,11,12,16] including those evaluations carried out in Mexico [5-7] (Table 4). Infections are the leading causes; although there is clearly a change toward atypical viral infections gaining on the formerly fre-quent bacterial infections like occult abscesses, bac-terial endocarditis, or gallbladder or urinary sepsis (Table 5). This shift could be linked with the use of more complex serologic tests, including those in which the viral genome is amplified; also the availability

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Table 5. FUO causes.

Final diagnosis	Frequency
INFECTION = 19 cases	
Acute HIV infection	4
CMV infection	2
Extrapulmonary tuberculosis	1
Pulmonary tuberculosis	1
Chronic bacterial meningitis	1
Pyogenic hepatic abscess	1
Bacterial subacute endocarditis	2
Brucelosis	2
Q fever	1
Salmonellosis	1
CNS cysticercosis	1
Pneumococcus sepsis	1
Staphylococcus phlebitis	1
INFLAMMATORY NON – INFECTIOUS = 12 cases	
Systemic lupus erythematosus	6
Polyarteritis nodosa	3
Dermatomyositis	1
Chron's disease	1
Lymphocytic vasculitis	1
MALIGNANCY = 8 cases	
Non-Hodgkin's lymphoma	6
Acute leukemia	1
Unknown primary adenocarcinoma	1
OTHER CAUSES = 1 case	
Aortic aneurysm	1
WITHOUT DIAGNOSIS = 5 cases	

of more accurate image studies, which disclose at a more early stage the presence of visceral lesions. On the other hand, there is an emerging number of non-infectious inflammatory conditions as a cause of classical FUO. Necrotizing vasculitis and systemic lupus erythematosus remain as the most frequent diagnosed autoimmune diseases; giant-cell arteritis, with a very low prevalence in Mexican patients, and adult Still disease, reported in other series were not found by us. Cancer is the third cause of classical FUO in this series, in agreement with other evaluations; non-Hodgkin's lymphoma contributes with the largest average of cases among the cancer group.

Other groups have been analyzed for clues that improve the diagnostic accuracy. De Kleijn and collaborators evaluated the potentially diagnostic contribution of some clues found during the first study week in 167 non-immune compromised patients;[17] however, such clues were frequently misleading and not related with improvement of accuracy. We believe that clinical or non-clinical data can be used in a different manner, namely to categorize patient into the main three dif-

ferent groups, and then guide studies of the second phase. LDH and fibrinogen serum levels, erythrosedimentation rate, age, and involuntary weight loss, were significantly different for each classical FUO diagnostic group in this series. A prospective analysis for this approach, evaluating a possible reduction of in-hospital days or economical costs, using these parameters to guide fever-study is warranted.

A special note is owed for the patients with no final diagnosis. These depict a wide variation between studies, from 11% in our series to 40% in Sheon's assessment[16]. The number of such cases depends on many factors; i.e., availability of diagnostic resources, or the proper skills of each health personnel team. It is our conviction, on the five cases in the category of no-diagnosis, that a prolonged non-recognized infection, perhaps of viral origin, could be responsible for the febrile illness. Cases in which a comprehensive evaluation is made and a definitive diagnosis is not reached are not necessarily linked to a worse prognosis or a severe disease. Our cases, for example, were followed by at least 30 months and no harmful illness developed in such time. Regarding this issue, Knockaert described a long-term assessment of patients with classical FUO and no definitive diagnosis: 19% could be diagnosed within the next two months; 51% remained free of symptoms during a 5-year follow-up; 30% had persisting fever, but disappeared in half the cases with no treatment; the remaining cases were empirically treated with corticosteroids having good results[18]

Finally, the problem of FUO requires to be evaluated in different communities, in order to underline the main differences among geographical areas in Mexico, social and cultural populations status, and the availability of medical technology. Besides, on a low-budget health program, the evaluation of the general cost of this syndrome is also mandatory, as well as to know the experience of second level and regional reference hospitals in Mexico, which has been scarcely published.

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