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Original article

Fever of unknown origin—predictors of outcome A prospective multicenter study on 164 patients

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Abstract

Background: To date, the studies that have been done on fever of unknown origin have mostly been descriptive. Therefore, we know the etiogical spectrum and how it has changed since 1966 for many regions of the world. However, we do not know if there are clinical or laboratory predictors of severe outcome. Being able to estimate the severity of the disease early on would allow one to determine how intensive the diagnostic work-up should be. *Methods:* A multicenter cohort study was carried out on 164 consecutive patients who met the classic, modified criteria of fever of unknown origin. The study lasted 2 years (1997–1998) and included a follow-up period of another 2 years. The main outcome measured was the final diagnosis established at the end of follow-up. *Results:* When the white cell count was abnormal, the relative risk for a serious disease was 1.49 (CI: 1.15–1.94; $p=0.004$), when anemia was present, the relative risk was 1.55 (CI: 1.21–1.98; $p=0.003$), and for high alanine aminotransferase (ALAT), bilirubin, or lactate dehydrogenase (LDH), the relative risks were 1.57 (CI: 1.21–2.02; $p=0.010$), 1.57 (CI: 1.18–2.08; $p=0.007$), and 3.43 (CI: 1.81–6.48; $p=0.0002$), respectively. In multivariate analysis, the odds ratios for serious diseases were 2.7 (CI: 1.17–6.4; $p=0.02$) for abnormal white cell count, 2.8 (CI: 1.14–7.16; $p=0.02$) for anemia, 4.3 (CI: 1.6–11.5; $p=0.003$) for high serum bilirubin, and 5.3 (1.5–18.6; $p=0.009$) for high serum ALAT. *Conclusions:* In patients having a fever of unknown origin, anemia, abnormal white cell count, and high ALAT and bilirubin are independent predictors of severe outcome.

Keywords: Multicenter cohort study; Prognosis; Fever of unknown origin; Bilirubin; Alanine aminotransferase; Lactate dehydrogenase; Anemia; Leukocytosis

1. Introduction

Fever of unknown origin (FUO) is extremely difficult to diagnose. It has been defined as an illness with a rectal temperature exceeding 38.3 °C on at least three occasions, lasting at least 3 weeks, and with no diagnosis reached after 1 week of intensive investigations [1]. Many prospective studies [2–10] of patients with FUO have been performed around the world using this definition, while other series have used different criteria. The spectrum of diseases seems to be determined by geographic and economic factors, and it appears to change with time. With

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the exception of a small retrospective study performed in a county hospital in Hungary [11], no other study on FUO has been performed in Central or Eastern Europe.

The question of how far we should proceed with invasive and/or expensive investigations when facing this diagnostic problem remains unanswered because of the descriptive nature of past studies, which assessed the spectrum of diseases causing FUO; none tried to determine whether it was possible to predict the severity of the outcome. Only one study developed a guide to predict the probability of reaching a diagnosis [12]. We therefore conducted a multicenter cohort study with a 2-year follow-up to determine the predictors of outcome of FUO in Romania.

2. Materials and methods

Of 37 departments of internal medicine and infectious diseases of university hospitals (secondary and tertiary care) from all regions of Romania that had been invited to participate in our study, nine eventually agreed to do so. A total of 164 patients were included in the 2-year study (January 1997–December 1998), as well as in the 2-year follow-up, which was conducted by telephone from the coordinating center to both the treating physicians and the patients themselves.

The inclusion criteria were: (a) age>18 years; (b) fever for at least 3 weeks; (c) fever>38.3 °C at least twice; (d) absence of diagnostic suggestions (diagnostic hypothesis) after history, clinical examination, and a series of screening investigations (Table 1); and (e) initial diagnostic hypothesis (raised after the history, clinical examination, and series of screening investigations) not confirmed after the appropriate investigations (a suggestions list was provided; Table 2). In order to be included, patients had to meet criteria (a)–(c) and either (d) or (e).

The exclusion criteria were: (a) immunosuppressive treatment within 2 months or granulocyte count $<10^9$/l for any reason; (b) known infection with HIV; (c) confirmation of the initial diagnostic hypothesis raised after history, clinical examination, and/or screening investigations.

Following the completion of some standard questionnaires, the medical history of each patient was taken and a thorough physical examination given.

Table 1
Screening investigations

1. Blood cell count + blood smear
2. Erythrocyte sedimentation rate
3. Serum creatinine, protein, albumin, glucose, bilirubin, alkaline phosphatase, aminotransferases, lactate dehydrogenase
4. Urinary analysis
5. Urine culture
6. Chest X-ray
7. Three blood cultures (aerobic + anaerobic)
8. Serum protein electrophoresis
9. C-reactive peptide

Medical history, physical examination, and the results of laboratory investigations were prospectively registered in a structured data collection form. In case of no diagnostic hypothesis, the tests listed in the two series of investigations (Table 3) were recommended.

At the end of follow-up, the patients were classified as having severe or mild illness. The inclusion criteria in the severe illness group were: (a) death due to the disease that had caused the FUO; (b) any neoplastic disease; (c) infections which, left untreated, invariably lead to death (septicemia, infectious endocarditis); and (d) severely altered general state and/or weight loss >5 kg.

Continuous variables were statistically analyzed and groups of patients (severe and mild illness) were first compared using the Mann–Whitney *U*-test. When the differences were statistically significant, the variables were transformed into dichotomous groups (e.g. normal/abnormal ALAT, LDH, hemoglobin). A two-tailed Fisher's exact test was used for all dichotomous variables in univariate analysis, and variables significant at the 0.1 level were then incorporated into a logistic regression model for multivariate analysis, with severity of disease (severe/mild) as the dependent variable. We used SPSS 11.0 software (SPSS, Chicago, IL, USA). The significance level (p) was set at 0.05.

3. Results

A total of 164 patients (85 females, 79 males) meeting our criteria for FUO were included in our 2-year study. Their mean age was 46.35 years (median 46 years, range 18–78 years).

A total of 93 patients (57%) were referred by general practitioners and 71 (43%) had already undergone extensive investigations before referral. The patients arrived after a mean of 97.73 days from the beginning of their FUO (median 49 days, range 3 days–3 years).

The mean follow-up was 19.49 months (median 22 months, range 1–24 months). Some 124 patients (75.6%) were followed for 24 months. For 33 patients (20.1%), the follow-up was less than 6 months. The follow-up of the 38 patients who died (23%) was considered to be 24 months.

Patients were hospitalized for a total of 3343 days, with a mean of 21.16 days per patient (median 19 days, range 5–69 days). The duration of hospital stay was not associated with the outcome ($p>0.05$).

A total of 133 patients (83%) had continuous fever and 27 (17%) had recurrent fever, the latter defined as at least two episodes of fever with intervals of at least 48 h without fever.

As for the etiology, 74 patients (45.1%) had infections, 41 (25%) neoplasms, 30 (18.3%) non-infectious inflammatory diseases, three (1.8%) drug fever, and four (2.1%)

Table 2
Investigations performed for the diagnostic hypothesis raised by the history, clinical examination, and/or screening investigations suggesting:

Giant cell arteritis, polymyalgia rheumatica: temporal artery biopsy.
Infectious endocarditis: echocardiography (transthoracic, transesophageal).
Hematologic disease: bone marrow puncture with or without culture (in case of suspected tuberculosis), bone marrow biopsy.
Pulmonary or mediastinal disease: tuberculin test, sputum culture for tuberculosis, pulmonary fibroscopy (broncho-alveolar lavage with cultures, cytologic exam), CT of chest.
Diarrhea: stools for worms, eggs, cysts, cultures; colonoscopy.
Abdominal disease: gynecologic exam, ultrasonography and/or CT of abdomen and pelvis.
Adenomegaly: biopsy, serologies for toxoplasma, CMV, HIV.
Thyroid disease: thyroid-stimulating hormone (TSH), T4; thyroid ultrasonography, antimicrosomal antibodies.
Collagen-vascular disease (skin manifestation, arthritis, serositis): antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic autoantibodies (ANCA), 24-h proteinuria, anti-double strained DNA (anti-dsDNA), cryoglobulins.
Liver disease: ultrasonography or CT, hepatitis B and C serologies, anti-smooth muscle and LKM antibodies, liver biopsy.
Sinus disease: radiograph of sinus and teeth.
Tooth disease: orthopantomogram.
Neuromuscular disease: lumbar puncture, brain CT, electromyogram (EMG), muscular biopsy, creatine phosphokinase.
Skin eruption: dermatologic exam, skin biopsy.
Paludism: thick blood smear.
Urinary disease: urinary quantitative and qualitative cytology, intravenous pyelography, urine cultures for tuberculosis.
Bilio-pancreatic disease: abdominal ultrasonography, CT, endoscopic retrograde colangiography.

Table 3
Proposed minimal investigations for patients with fever of unknown origin

First series
Tuberculin test
24-h Proteinuria
Antinuclear antibodies, anti-dsDNA
Bence-Jones proteinuria
Abdomino-pelvic ultrasonography
Sinus X-ray
Orthopantomogram
Temporal artery biopsy (if age >60)
Bone marrow puncture (if hematological perturbation: leukopenia, thrombocytopenia, anemia, peripheral abnormal cells)
B and C hepatitis, HIV, CMV serologies
Thyroid-stimulating hormone
Transthoracic echocardiography
Gynecologic exam
Second series (if examinations of first series are negative):
Chest, abdominal, and pelvic CT scan
Liver biopsy (if high aminotransferases)
Bone marrow puncture
Bone marrow biopsy (in case of hematological perturbation and/or high LDH)
Colonoscopy
Small intestine radiological exam

other causes. The etiology remained obscure for 12 patients (7.3%); the fever disappeared spontaneously in nine patients, one patient still had fever at the end of follow-up, and the fever disappeared in two patients after empirical treatment with corticosteroids, which was initiated because of the severity of their illness.

The most frequent etiologies were tuberculosis ($n=27$, 16.5%), malignant lymphoma ($n=21$, 13%), and collagen-vascular diseases ($n=17$, 10.3%).

Using the criteria presented in the Materials and methods section at the end of follow-up, 93 patients (56.7%) were classified as having a severe illness and 71 patients (43.3%) as having a mild illness (Table 4).

In univariate analysis, anemia, abnormal white blood cell count, and increased alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), and total bilirubin were associated with an increased risk of severe illness (Table 5), whereas the age of patients, duration of fever, serum albumin, and erythrocyte sedimentation rate (ESR) were not.

In multivariate analysis by logistic regression, the model retained four independent variables: anemia, leukocytosis, high ALAT, and high total bilirubin (sample size: 120 patients; Table 6). Unfortunately, LDH could not be introduced into the model because of the high number of missing values.

Table 4
Classification of outcomes in severe and not severe disease

Severe outcome		Mild outcome	
Lymphoma	21	Tuberculosis	16
Solid neoplasm	12	FUO[c]	10
Collagen-vascular disease[a,b]	11	Chronic pyelonephritis	7
Tuberculosis[a]	11	Giant cell arteritis	6
Infectious endocarditis	8	Collagen-vascular disease	5
Leukemia	8	Adult Still's disease	4
AIDS	4	Drug fever	3
Typhoid fever	4	Dental infection	3
Acute pyelonephritis	3	Toxoplasmosis	2
FUO[a,c]	2	Cytomegalovirus infection	2
Cholecystitis	2	Mycoplasma pneumoniae	2
Chronic pyelonephritis[a]	2	Cryoglobulinemia	2
Septicemia	2	Hyperthyroidism	2
Encephalitis	2	Pneumonia	2
Giant cell arteritis[d]	1	Neurosis[e]	2
		Probably infectious FUO[f]	2
		Rheumatoid arthritis	1
Total	93	Total	71

[a] Altered general state and/or weight loss >5 kg.
[b] Systemic lupus erythematosus, polymyositis, dermatomyositis, overlap syndrome.
[c] Undiagnosed FUO.
[d] The patient had amaurosis and weight loss >5 kg.
[e] The patients had normal clinical and laboratory examinations (excepting neurosis) and the fever disappeared after sedative therapy.
[f] Undiagnosed FUO that resolved with antibiotherapy.

The equation of the logistic regression was:

$$\begin{aligned}\text{LOGODDS (severe illness)} = &-1.1275 + 1.4678 \\ &\times (\text{bilirubin}) + 1.6677 \\ &\times (\text{ALAT}) + 1.0519 \\ &\times (\text{anemia}) + 1.0078 \\ &\times (\text{leukocytosis}).\end{aligned}$$

Estimated from this equation, the patient's risk for a severe illness was equal to 24% when all variables (red cell and white cell count, ALAT, and bilirubin) were within the normal range, and equal to 98% when all variables were pathologic.

4. Discussion

We performed a multicenter cohort study in order to obtain a representative sample of patients with FUO in our country. We did not succeed in including all patients with FUO, although all university hospitals were invited to participate. However, this is the first multicentric, prospective study on the subject in Romania, and patients from all regions of the country were included.

Because of the imprecision of Petersdorf's third criterion [1], which could lead to selection bias, we tried to change it from a time-related to a quality-related criterion. Our study had already begun when newer definitions of FUO were discussed [13,14].

The etiology of FUO in Romania respected the classical triad (infections, neoplasms, and non-infectious inflammations) present in other studies, with the proportions being equivalent to those in older Western series [1,3], in series from community hospitals [6], and in the newer series from the developing world [10]. We found a large proportion of infections dominated by tuberculosis, due to its high incidence in Romania, and an important proportion of solid neoplasms and systemic lupus erythematosus, partly due to the low access to imaging techniques (ultrasonography and computed tomography) and specific serologic procedures during the first week of investigations.

All of the existing studies were purely descriptive, except for one [12], which developed a guide for predicting the probability of reaching a diagnosis. According to this guide, the probability of reaching a diagnosis is higher when the patient has continuous rather than periodic fever and/or anemia and/or abnormal serum protein electrophoresis.

We considered that when a patient with an FUO is seen for the first time, it is most important to predict the severity of the outcome. Depending on the potential predictors, the clinician should decide (a) whether he should continue with more and more expensive and invasive investigations or (b) if he can confine himself to clinical examination and

Table 5
Predictors of severe outcome (univariate analysis)

Parameter	Severe outcome	Mild outcome	Relative risk with confidence interval	Test	*p* (two-sided)	Sample[a], *n*
Age (years)	51[b] (18–78)[c]	40[b] (18–77)[c]		Mann–Whitney *U*	0.114	164
Duration of fever (days)	47[b] (3–700)[c]	52[b] (4–1000)[c]		Mann–Whitney *U*	0.136	164
ESR (mm/h)	85[b] (5–175)[c]	79[b] (2–150)[c]		Mann–Whitney *U*	0.252	160
Serum albumin (g/dl)	3.4[b] (1.9–4.5)[c]	3.4[b] (1.7–4.8)[c]		Mann–Whitney *U*	0.591	144
Anemia (Hb<10 g/dl)	35/91 (38.4%)	11/69 (15.9%)	1.55 (1.21–1.98)	Fisher's exact test	0.003	160
High ALAT	18/87 (20.7%)	4/67 (6%)	1.57 (1.21–2.02)	Fisher's exact test	0.010	154
High LDH	12/20 (60%)	2/26 (7.7%)	3.43 (1.81–6.48)	Fisher's exact test	0.0002	46
High bilirubin	26/68 (38.2%)	8/52 (15.4%)	1.57 (1.18–2.08)	Fisher's exact test	0.007	120
Leukocytosis ($>10^{10}$/l)	46/91 (50.5%)	19/69 (27.5%)	1.49 (1.15–1.94)	Fisher's exact test	0.004	160
Chills	26/93 (28%)	23/71 (32.4%)	0.91 (0.67–1.2)	Fisher's exact test	0.607	164
Perspiration	69/93 (74.2%)	47/70 (67.1%)	1.2 (0.83–1.7)	Fisher's exact test	0.383	163
Continuous vs. recurrent fever	15/91 (16.5%)	12/69 (17.4%)	1.0 (0.7–1.4)	Fisher's exact test	1	160

[a] Without missing values.
[b] Median.
[c] Range.

a basic series of investigations, and then wait for new clinical clues to appear.

In this study, anemia, leukocytosis, abnormal ALAT, and abnormal bilirubin predicted a severe illness as the cause of FUO, both in univariate and multivariate analysis. ALAT and bilirubin were independent predictors of severity, as there was no correlation between them (the correlation matrix was performed to exclude multicollinearity). Therefore, we cannot replace ALAT and bilirubin with hepatic damage as an independent variable.

In multivariate analysis, a part of the constant may be explained by LDH, which in univariate analysis was

Table 6
Factors associated with a severe outcome of FUO (multiple logistic regression)

Variable	Coefficient	Standard error	*p*-value	Odds ratio	Upper 95% confidence interval	Lower 95% confidence interval
High total bilirubin	1.4678	0.4984	0.0032	4.3395	1.6338	11.5260
High ALAT	1.6677	0.6409	0.0093	5.2999	1.5093	18.6108
Hemoglobin <10 g/dl	1.0519	0.4680	0.0246	2.8632	1.1442	7.1644
Leukocytes $>10^{10}$/l	1.0078	0.4333	0.0200	2.7396	1.1718	6.4049

Likelihood ratio test: $P=0.0001$; Hosmer-Lemeshow goodness-of-fit test: $P=0.1118$.

associated with the highest relative risk for a severe outcome (LDH could not be introduced into the multivariate model because of the important number of missing values). On the other hand, multivariate analysis by logistic regression suggests that when all the variables of the multivariate model are pathologic, the probability of a severe outcome is 98%; therefore, the additive predictive value of elevated LDH may be of little relevance.

When the patient has normal hemoglobin, a normal white cell count, and normal ALAT, LDH, and bilirubin, the probability of having a severe disease is low. Therefore, we propose that, at the first visit, the physician should confine himself to clinical examination, a few investigations (those in Table 1 plus abdominal ultrasonography and antinuclear antibodies), and the patient's follow-up. In contrast, anemia, an abnormal white blood count, and especially high LDH, ALAT, and bilirubin are predictors of severe disease, and intensive diagnostic work-up is necessary when these abnormalities are present. Based on these rules, we plan to implement a second prospective study and to assess the validity of these recommendations in clinical practice.

In conclusion, our results indicate that, in patients presenting with FUO, anemia, an abnormal white cell count, and high ALAT and bilirubin are independent predictors of severe outcome.

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References

[1] Petersdorf RG, Beeson P. Fever of unexplained origin: report of 100 cases. Medicine 1961;40:1–30.
[2] Gleckman RA, Crowley M, Esposito A. Fever of unknown origin: a view from the community hospital. Am J Med Sci 1977;274:21–5.
[3] Howard P, Hahn H, Palmer RL, Hardin WJ. Fever of unknown origin: a prospective study of 100 patients. Texas Med 1977;73:56–9.
[4] Larson EB, Featherstone HJ, Petersdorf RG. Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970–1980. Medicine 1982;61:269–92.
[5] Barbado FJ, Vazquez JJ, Pena JM, Arnalich F, Ortiz-Vazquez J. Pyrexia of unknown origin: changing spectrum of diseases in two consecutive series. Postgrad Med J 1992;68:884–7.
[6] Kazanjian PH. Fever of unknown origin: review of 86 patients treated in community hospitals. Clin Infect Dis 1992;15(6):968–73.
[7] Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s. An update of the diagnostic spectrum. Arch Int Med 1992;153:52–5.
[8] Shoji S, Imamura A, Imai Y et al. Fever of unknown origin: a review of 80 patients from the Shin'etsu area of Japan from 1986–1992. Int Med 1994;33(2):74–6.
[9] The Netherlands FUO Study Group, de Kleijn EMHA, Vandenbroucke JP, van der Meer JWM. Fever of unknown origin (FUO) I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. Medicine 1997;76:392–400.
[10] Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. J Postgrad Med 2001;47(2):104–7.
[11] Almasi I, Ternak G. Differential diagnosis in patients with fever at the department for infectious diseases of a county hospital. Orv Hetil 1993;133:159–62.
[12] The Netherlands FUO Study Group, de Kleijn EMHA, van Lier HJ, van der Meer JWM. Fever of unknown origin (FUO) II. Diagnostic procedures in a prospective multicenter study of 167 patients. Medicine 1997;76:401–14.
[13] Arnow PM, Flaherty JP. Fever of unknown origin. Lancet 1997;350:575–80.
[14] de Kleijn EMHA, Knockaert DC, van der Meer JWM. Fever of unknown origin: a new definition and proposal for diagnostic work-up. Eur J Int Med 2000;11:1–3.