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The spectrum of diseases causing fever of unknown origin in Turkey: a multicenter study

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Summary
Objective: The purpose of this trial was to determine the spectrum of diseases with fever of unknown origin (FUO) in Turkey.
Methods: A prospective multicenter study of 154 patients with FUO in twelve Turkish tertiary-care hospitals was conducted.

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Results: The mean age of the patients was 42 ± 17 years (range 17—75). Fifty-three (34.4%) had infectious diseases (ID), 47 (30.5%) had non-infectious inflammatory diseases (NIID), 22 (14.3%) had malignant diseases (MD), and eight (5.2%) had miscellaneous diseases (Mi). In 24 (15.6%) of the cases, the reason for high fever could not be determined despite intensive efforts. The most common ID etiologies were tuberculosis (13.6%) and cytomegalovirus (CMV) infection (3.2%). Adult Still's disease was the most common NIID (13.6%) and hematological malignancy was the most common MD (7.8%). In patients with NIID, the mean duration of reaching a definite diagnosis (37 ± 23 days) was significantly longer compared to the patients with ID (25 ± 12 days) ($p = 0.007$). In patients with MD, the mean duration of fever (51 ± 35 days) was longer compared to patients with ID (37 ± 38 days) ($p = 0.052$).

Conclusions: Although infection remains the most common cause of FUO, with the highest percentage for tuberculosis, non-infectious etiologies seem to have increased when compared with previous studies.

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Introduction

The spectrum of diseases causing fever of unknown origin (FUO) not only seems to be determined by the geographic region, age of the patient, type of healthcare facility, and socioeconomic status of the country, but also appears to be changing over time owing to the net effect of complex inter-actions between all these parameters.[1,2] Thus, clinicians may find it difficult to establish the entire spectrum of diseases causing FUO. A satisfactory standardization has not yet been achieved, because studies in this area have used either a retrospective design[3,4] or variable diagnostic criteria.[5,6]

Although some suggestions have been made on diagnosis, it has been impossible to extrapolate these approaches.[7—9] Prospective studies performed using uniform criteria have failed to provide a satisfactory methodology for FUO cases in developing countries where diagnostic tools are usually una-vailable. In Turkey, in particular, failure to implement stan-dardized diagnostic criteria in studies performed so far, and the lack of prospective multicenter studies, have precluded comprehensive evaluations of the current situation in the country as a whole.

This study was performed prospectively to obtain more comprehensive data on FUO throughout the country in order to establish the changing spectrum of FUO and to determine diagnostic clues by using objective criteria in healthcare settings such as tertiary-care hospitals, where conventional modern diagnostic tools are more commonly used.

Patients and methods

This study was conducted prospectively in twelve Turkish tertiary-care hospitals between January 2003 and June 2004. Medical records of all patients with an initial diagnosis of FUO were retrieved from a computer database generated for this study. All cases were followed up in a hospital setting and written informed consent was obtained. Patients enrolled in this study were older than 18 years of age and fulfilled the modified Petersdorf criteria of FUO.[10,11] These criteria are: (1) a temperature exceeding 38.3 °C; (2) duration of the fever of more than three weeks; (3) evaluation of three outpatient visits or three days in hospital.

Initially, patient complaints along with personal and family histories, travel history, occupation, and results of physical exam were noted. At least two blood cultures were obtained from two different extremities at a 30-minute interval for each patient during the fever episode. Patients with non-diagnostic initial laboratory tests underwent further laboratory testing. Symptoms and signs of all patients were recorded. The same attending physicians performed regular visits to evaluate daily changes for all patients. The diagnostic protocol was applied to all patients (Table 1). Abnormal tests were subdivided into 'contributing' and 'non-contributing'. The cause of FUO was determined at the time of discharge or during follow-up. The causes were classified into five groups: (1) infectious diseases (ID), (2) malignant diseases (MD), (3) non-infectious inflam-matory diseases (NIID), (4) miscellaneous (Mi), and (5) undiag-nosed (U).

The day of hospital admission was nominated as the first day for the follow-up of symptoms and signs. Clinical and laboratory data obtained before admission were used only as complementary data. Evaluation of the course of fever was also started from the day of admission. Patients ceased using any antibiotics or antipyretics on the admission day.

Statistical analysis

Most variables showed non-normal distribution, thus non-parametrical methods were used in all analyses. Values were compared using Kruskal—Wallis non-parametric ANOVA. The patients were dichotomized into diagnosis groups (i.e., patients with or without 'infection', etc.) and then mean values were compared using the Mann—Whitney U test.

Group percentages were compared using contingency table analyses, Chi-square test, Fisher's exact test, and Mantel—Haenszel test. The association between factors and diagnoses were analyzed by means of multivariate logis-tic regression analysis. A value of $p < 0.05$ was considered significant, except in stepwise logistic regression models. For the latter, a value of $p < 0.10$ was considered significant. No adjustments were done for multiple tests.

Results

During the study period, 154 patients meeting the FUO criteria were evaluated in 12 tertiary-care hospitals. The mean age of the patients was 42 ± 17 years (range 17—75).

Table 1 Diagnostic protocol

Complaints

History
    Personal history
    Family history

Evaluation of systems
Physical exam
Appropriate tests if there are any diagnostic clues
If no clues, start diagnostic workup with first-line tests
No diagnosis with first-line tests, continue with second-line tests
Definitive diagnosis with positive serology or positive
    culture or histology

In some patients:
    by excluding other diseases
    by a response to specific treatment, or
    by observing the course of the disease

Definitive diagnosis made by the attending physician or by the consultants he/she has chosen
The time and type of diagnosis recorded. Number and time of tests and radiographic methods checked in patient files
Patients with no definitive diagnosis followed up, even after discharge, for 6 months
Daily physicals continue during diagnostic work-up with recording of any changes that occur

Phase 1 diagnostic protocol:
    Complete blood count with differential, ESR, CRP, RF, ASO, CMV IgM, EBV IgM, urinanalysis, HBsAg, glucose, uric acid,
        AST, ALT, GGT, LDH, ALP, T-bilirubin, D-bilirubin, albumin, T-protein, BUN, creatinine, Na, K, Ca, CPK, ANA, ds-DNA,
        TSH, PPD, Brucella agglutination, Salmonella agglutination, cultures of blood, urine, stool, and sputum, stool microscopy,
        AARB in sputum, chest X-ray, abdominopelvic US

Phase 2 diagnostic protocol:
    Protein electrophoresis, amylase, ACE, ANCA, IgG, IgA, IgM, ENA panel, C3, C4, cryoglobulin, T3, T4, Mycoplasma
        cell culture, Toxoplasma cell culture, Treponoma, Yersinia cell cultures, lymph node biopsy and culture, liver biopsy,
        temporal artery biopsy, thyroid biopsy, VMA in 24-hour-urine, thyroglobulin, antimicrosomal antibody, PSA, HIV, HCV,
        plasma cortisol, echocardiography, abdomino-pelvic CT, chest CT, rectosigmoidoscopy, barium enema, sinus X-ray,
        dental exam, fundic exam, leukocyte scan, laparoscopy, laparatomy

Phase 3 diagnostic protocol:
    Invasive procedures: all kinds of biopsies, laparoscopy/laparatomy, endoscopic examinations
    Non-invasive procedures: hematologic, serologic tests, cultures, radiologic examinations

AARB, acid–alcohol resistant bacilli; ACE, angiotensin-converting enzyme; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; ASO, antistreptolysin O; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C3, C4, complement; CMV, cytomegalovirus; CPK, creatinine phosphokinase; CRP, C-reactive protein; CT, computerized tomography; D-bilirubin, direct bilirubin; ds-DNA, double-stranded DNA; EBV, Epstein–Barr virus; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; GGT, γ-glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; PPD, purified protein derivative; PSA, prostate-specific antigen; RF, rheumatoid factor; T3, triiodothryronine; T4, thyroxine; T-bilirubin, total bilirubin; T-protein, total protein; TSH, thyroid stimulating hormone; US, ultrasound; VMA, vanillylmandelic acid.

Eighty-three (53.9%) patients were male and 71 (46.1%) were female. The final diagnoses are shown in Table 2.

The mean duration of fever in patients in whom a diagnosis was established was 35 ± 32 days (range 13–180). In patients with MD, the mean duration of fever (51 ± 35) was longer than for those with ID (37 ± 38) ($p = 0.052$), although this difference was not statistically significant. The mean interval between admission and diagnosis was 32 ± 18 days (range 4–90 days). In NIID patients this interval (37 ± 23) was significantly longer than in patients with ID (25 ± 12) ($p = 0.007$).

The most common risk factors in our cases were previous use of antibiotics, history of cigarette smoking, and previous diseases. Compared to other groups, a history of previous antibiotic use was significantly more common in the Mi group ($p = 0.027$).

Symptoms and signs

The most common symptoms were fever (100%), fatigue (80%), chills (67%), weight loss (62%), myalgia (44%), and arthralgia (4%). Weakness was observed significantly more frequently in the MD and ID groups ($p = 0.019$ and $p = 0.013$, respectively). In NIID and MD groups, arthralgia was more common than in the others ($p = 0.015$ and $p = 0.001$, respectively).

The mean value of fever was $38.3 \pm 0.3\,^{\circ}$C at the first examination with no significant difference between the groups. The most common physical findings were cardiac murmur (27%), hepatomegaly (23%), lymphadenomegaly (22%), skin rash (16%), splenomegaly (15%), and arthritis (13%).

Table 2 The final diagnosis in patients with fever of unknown origin

Infectious diseases (53)	Malignant diseases (22)	Non-infectious inflammatory diseases (47)	Miscellaneous (8)
Tuberculosis (21)	**Hematological malignancies (12)**	**Collagen tissue disease (31)**	Drug fever (2)
Pulmonary tuberculosis (6)	Hodgkin lymphoma (4)	Adult Still's disease (21)	FMF (2)
Disseminated tuberculosis (5)	Non-Hodgkin lymphoma (1)	Subacute thyroiditis (3)	Ulcerative colitis (1)
Tuberculosis lymphadenitis (5)	Splenic lymphoma (2)	SLE (2)	Crohn's disease (1)
Pleural tuberculosis lymphadenitis (2)	Multiple myeloma (2)	Dermatomyositis (1)	Thrombosis (1)
Pericardial tuberculosis (1)	CML (1)	Rheumatoid arthritis (1)	Gout (1)
Renal tuberculosis (1)	MDS (1)	Polymyositis (1)	
Peritoneal tuberculosis (1)	AML (1)	Polymyalgia rheumatica (1)	
Other (32)	**Solid cancer (10)**	Interstitial pulmonary fibrosis (1)	
CMV pneumonia (5)	Adenocarcinoma (2)	**Vasculitis (14)**	
Abscesses (5)	Stromal tumor (1)	Unclassified vasculitis (5)	
Brucellosis (5)	Hypernephroma (1)	Temporal arteritis (4)	
Toxoplasmosis (4)	Castleman disease (1)	PAN (3)	
Salmonellosis (3)	Metastatic carcinoma (1)	HSP (2)	
Pyelonephritis (2)	Testis tumor (1)	**Granulomatous disease (2)**	
PID (2)	Colon carcinoma (1)	Sarcoidosis (2)	
Urinary infection (2)	Pancreatic carcinoma (1)		
Endocarditis (1)	Gastric carcinoma (1)		
Systemic candidiasis (1)			
Leptospirosis (1)			
Meningitis (1)			

Undiagnosed (24)

CMV, cytomegalovirus; PID, pelvic inflammatory disease; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; AML: acute myeloid leukemia; SLE, systemic lupus erythematosus; PAN, polyarteritis nodosa; HSP, Henoch—Schönlein purpura; FMF, familial Mediterranean fever.

Biochemical techniques

The most frequent chemical findings were elevated erythrocyte sedimentation rate (ESR) (88%), elevated C-reactive protein (CRP) (80%), elevated γ-glutamyl transpeptidase (GGT) (68%), anemia (64%), and leukocytosis (50%) (Table 3). Initially 2978 biochemical tests were performed. Of 1080 positive biochemical tests, only 18 (1.7%) contributed indirectly to diagnosis.

Microbiologic serology

Sixteen of 752 serologic tests yielded significant results for a definite diagnosis. The diseases most commonly diagnosed by serologic tests were cytomegalovirus (CMV) infections, brucellosis, salmonellosis, and *Mycoplasma pneumoniae* infections. CMV seropositivity was identified in five cases. In four of these patients mononucleosis-like clinical presentation was observed, and two of them also had histopathologic findings concordant with CMV. Successive serologic tests repeated at 10-day intervals revealed a course of IgM- and IgG-type antibodies, which was compatible with acute infection. In all patients with positive Mycoplasma serology, pulmonary findings were identified either before or shortly after the diagnosis. All cases had atypical pneumonia. Our salmonellosis cases came to us very late and possibly after the bacteremic period; cultures were negative, albeit the serology was positive with high titers.

Immunologic serology

Of the 156 immunoserologic tests, 20 yielded positive results and eight of these were considered 'contributing'. The results of the immunologic examinations were as follows (positive results/number of tests): antinuclear antibody (ANA; 10/145), double-stranded DNA (ds-DNA; 2/94), rheumatoid factor (RF; 2/48), extractable nuclear antigen (ENA; 4/38), angiotensin-converting enzyme (ACE; 1/14), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA; 1/9), and immunoelectrophoresis (-/8). ANA and ds-DNA were helpful in establishing the diagnosis of systemic lupus erythematosus (SLE; $n = 2$), whereas RF was helpful in diagnosing vasculitis in rheumatoid arthritis.

Culture techniques

From 514 cultures obtained from all patients the following results were revealed (positive results/number of tests): blood (8/154), urine (7/154), sputum (4/128), stool (1/22), wound (4/15), catheter (2/12), pleural fluid (2/10), cerebrospinal fluid (-/10), and peritoneal fluid (-/9). Results of 12 cultures (six blood, three urine, two sputum, one pleural fluid) revealed the final diagnosis.

In six patients, blood cultures were used to establish the diagnosis: abscesses in three patients, pneumonia with bacteremia in two patients, and tuberculosis in one patient. In four patients, false-positive blood cultures were obtained by

Table 3 Laboratory findings

	N (%)	ID %	MD %	NIID %	Mi %	U %	p
ESR >20 mm/h	136 (88)	81	90	100[a]	92	75[b]	[a]p = 0.003 [b]p = 0.027
ESR (mean ± SD)	76 ± 38	75 ± 39	70 ± 42	88 ± 32[a]	46 ± 9[b]	73 ± 41	[a]p = 0.019 [b]p = 0.011
CRP >6 mg/dl	124 (80)	79	77	82	75	83	NS
CRP (mean ± SD)	50 ± 59	49 ± 61	29 ± 49[a]	64 ± 63[b]	47 ± 63	42 ± 49	[a]p = 0.019 [b]p = 0.006
GGT >50 U/l	102 (68)	71	71	71	71	16[a]	[a]p = 0.039
Anemia <12 g/dl	100 (64)	64	72	62	20	87[a]	[a]p = 0.027
Hb g/dl	10.7	10.7	9.7[b]	10.9	13.4[a]	10.4	[a]p = 0.001 [b]p = 0.027
Leukocytosis >10 × 10^9/l	78 (50)	42	63	65[a]	75	20[b]	[a]p = 0.001 [b]p = 0.001
Leukocyte count (×10^9/l)	12.956	10.519	21.977	13.845	10.905	9.149	NS
ALP >160 U/L	74 (48)	55	54	47	12	37	NS
BUN >20 mg/dl	67 (43)	50	54	43	50	16[a]	[a]p = 0.004
LDH >450 U/l	62 (40)	42	40	37	12	50	NS
LDH (mean ± SD)	505 ± 381	502 ± 364	651 ± 535[a]	441 ± 203		447 ± 127	[a]p = 0.035
Hyperuricemia	38 (40)	58[a]	28	47	0	12[b]	[a]p = 0.038 [b]p = 0.012
ALT >40 U/l	57 (37)	42	45	39	25	16[a]	[a]p = 0.025
ALT (mean ± SD)	48 ± 59	42 ± 36	65 ± 92	51 ± 66	26 ± 20	44 ± 57	NS
AST >40 U/l	53 (34)	39	36	34	25	25	NS
Proteinuria	38 (24)	26	18	30		25	NS
Total bilirubin >1 mg	18 (13)	15	10	13		8	NS
Hematuria	14 (9)	7		13	25	8	NS
CPK >190 U/l	10 (6)	2	4	13[a]	12	4	[a]p = 0.031

ID, infectious diseases; MD, malignant diseases; NIID, non-infectious inflammatory diseases; Mi, miscellaneous; U, undiagnosed; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; GGT, γ-glutamyl transpeptidase; Hb, hemoglobin; ALP, alkaline phosphatase; BUN, blood urinary nitrogen; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; NS, not significant.

the growth of coagulase-negative staphylococci. Urinary cultures were helpful in establishing the diagnosis in three patients.

Sputum samples were helpful in establishing the diagnosis in two patients with pneumonia. Two patients were considered false-positive. Among 28 positive culture results, 12 contributed to the FUO diagnosis.

Imaging techniques

A chest X-ray was obtained from all patients and contributed to the diagnosis in 13 patients, leading the clinicians to more specific diagnostic approaches. Although chest X-ray is not diagnostically instructive in the evaluation of FUO,[12] this test was performed as an initial diagnostic test within the first three days of hospitalization when the patient was not categorized as an FUO case. Tuberculosis (8), pneumonia (3), Hodgkin lymphoma (1), and sarcoidosis (1) were detected as the final diagnoses in these patients.

Ultrasound (US) was performed in 141 patients. US contributed to diagnosis in seven patients: hepatic abscess (2), retroperitoneal abscess (1), liver metastasis (1), hypernephroma (1), pyelonephritis (1), and splenic lymphoma (1). Abdominal computerized tomography (ACT)

was performed in 98 patients and contributed to the diagnosis in 10 patients: solid cancer (3; hepatoma, pancreas cancer, hypernephroma), hepatic abscess (2), retroperitoneal abscess (1), pelvic abscess (1), liver metastasis (1), splenic lymphoma (1), multiple myeloma (1). Thorax computerized tomography (TCT) was performed in 82 patients. TCT contributed to diagnosis in five patients: sarcoidosis, pneumonia, tuberculosis, lymphoma, interstitial pulmonary fibrosis (one patient each). Trans-thoracic echocardiography (TTE) was performed in 82 patients. TTE contributed to the diagnosis of two patients (tuberculous pericarditis, infective endocarditis). Brain computerized tomography (BCT) was performed in 20 patients. BCT contributed to the diagnosis of two patients: cerebral infarction (vasculitis case) and neurobrucellosis. Colonography with barium enema (n = 15) contributed to diagnoses in two patients: colon carcinoma and ulcerative colitis. Intravenous pyelography (n = 5) contributed to only one diagnosis: ureteral obstruction in pelvic abscesses. Doppler ultrasound (n = 10) contributed to the diagnosis in only one patient: venous thrombosis.

Six hundred and seven radiological tests were performed; of these tests, 43 contributed to the diagnosis. One hundred and forty-one tests were considered as 'non-contributing'.

Table 4 Diagnostic values of the histologic techniques

Histologic techniques (positive/total)	Final diagnosis
Lymph node biopsy (9/20)	Tuberculosis lymphadenitis (5)
	Lymphoma (3)
	Castleman disease (1)
Thyroid biopsy (3/8)	Subacute thyroiditis (3)
Bone marrow aspiration (2/5)	Chronic myelocytic leukemia (1)
	Multiple myeloma (1)
Bone marrow biopsy (5/17)	Multiple myeloma (1)
	Acute myeloid leukemia (1)
	Lymphoma (2)
	Myeloid syndrome (1)
Liver biopsy (5/14)	Granulomatous hepatitis (2)
	Hepatoma (1)
	Metastatic adenocarcinoma (1)
	Candida infection (1)
Skin biopsy (3/12)	Henoch—Schönlein purpura (1)
	Dermatomyositis (1)
	Hypersensitivity vasculitis (1)
Temporal artery biopsy (4/16)	Temporal arteritis (4)
Upper gastrointestinal endoscopy and/or colonoscopy with biopsy (2/41)	Gastric carcinoma (1)
	Colon carcinoma (1)
Pancreatic biopsy (1/2)	Pancreatic carcinoma (1)
Renal biopsy (1/1)	Hypernephroma (1)
Peritoneal biopsy (1/1)	Tuberculosis peritonitis (1)
Pleural biopsy (1/1)	Pleura tuberculosis (1)
Lumbar puncture (1/12)	Meningitis (1)
Thorasynthesis, pericardiosynthesis and/or parasynthesis (3/19)	Tuberculosis (2)
	Intra-abdominal abscesses (1)

Histologic techniques

Histologic examinations were performed in 143 patients and 41 biopsies yielded results contributing to the diagnosis. Of these, nine were obtained from lymph nodes, three from thyroid gland, five from bone marrow, five from liver, three from skin, and four from temporal artery biopsies (Table 4).

Compared to the other groups, the diagnostic utility of culture results was significant in the ID group ($p = 0.001$), immunologic assessments were significant in the NIID group ($p = 0.02$), and radiologic and histopathologic methods were especially significant for the MD group ($p = 0.016$ and $p = 0.002$, respectively). The diagnostic utility of clinical observations was significant in the NIID and MD patients ($p = 0.001$ and $p = 0.031$, respectively).

The cause of FUO was diagnosed by non-invasive techniques in 78 patients and by invasive procedures in 52 patients.

Infectious diseases (ID) group

The most common symptoms in the ID group were fatigue, chills, weight loss, nausea, and headache. The most commonly observed physical examination findings were cardiac murmur, hepatomegaly, and lymphadenopathy. Nausea, abdominal pain, and diarrhea complaints were common compared to the other groups ($p < 0.05$.). The mean level of fever was $38.4 \pm 0.7\,^{\circ}$C, and the fever level was found to

be significantly higher in the ID group compared to the other groups at weeks 2 and 4 (Figure 1). In the MD group the number of cases with leukocytosis increased in weeks 4—6, but decreased in the ID group ($p = 0.013$; Figure 2).
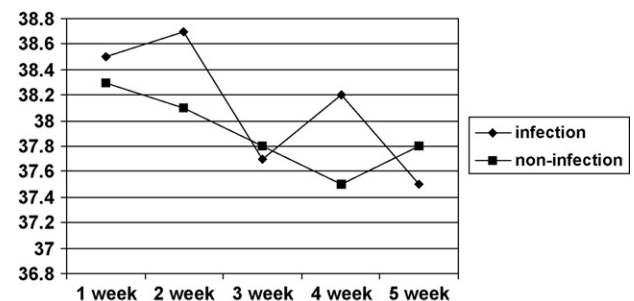

Figure 1 Mean values of fever in the infectious diseases (ID) and other non-infectious groups.
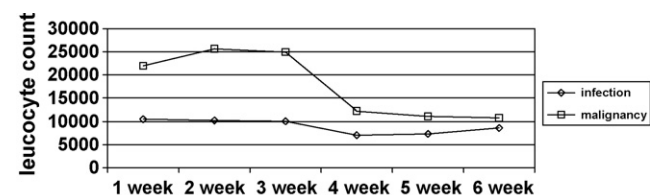

Figure 2 Median leukocyte counts in the infectious diseases (ID) and malignant diseases (MD) groups.

The diagnosis of infections was established by blood cultures in 10% of cases, by invasive procedures in 29% of cases, and by serologic test results in 22% of cases. The mean time to diagnose ID cases was 25 ± 12 days and was significantly shorter than in the other groups (p = 0.05). In nine tuberculosis cases (42.9%), biopsy was diagnostic (five tuberculosis lymphadenitis, two liver biopsies, one peritoneal and one pleural biopsy). In six cases (28.6%), radiology plus clinical findings (five chest X-rays, one pulmonary CT) were diagnostic. In four cases (19.0%), positive acid resistant bacteria (one blood, one urine, one sputum, one pleural fluid) was diagnostic, in one case echocardiography was diagnostic, and in another case clinical observation plus treatment established the diagnosis.

Among abscess cases, three were diagnosed by US (two hepatic, one pelvic) and two by CT (one hepatic, one retroperitoneal). The presence of concomitant diseases, nausea, high-grade fever, higher respiration rate, and more diarrheic complaints were independent risk factors for the ID group.

Malignant diseases (MD) group

The most common symptoms in the MD group were fatigue, weight loss, and tachycardia. The mean value of fever was $38.5 \pm 0.5\,^\circ$C and the mean number of days with fever was 51 ± 35. The number of days with fever was higher in the MD group compared to the other groups (p = 0.031). The median leukocyte values were significantly higher than the values of the infection group ($p < 0.005$; Figure 2).

Mean CRP values were 29 ± 49 in the MD patients. Compared to the other groups, the CRP level was lower. Mean CRP values continued a lower course also in the following weeks ($p < 0.05$). All cases of solid cancer (n = 10) were diagnosed by biopsy. In this group, the diagnostic utility of radiological examinations and biopsy was high. The mean hemoglobin level was low and the mean lactic dehydrogenase level was higher. The mean total protein level was lower (6.2 ± 0.7, p = 0.039).

Non-infectious inflammatory diseases (NIID) group

The most common symptoms in the NIID group were fatigue, arthralgia, and myalgia. In this group, the percentages of muscle pain and arthralgia, skin lesions and arthritis, and pathologic findings on fundoscopic examination were higher. Among laboratory findings, leukocytosis, elevated ESR, elevated creatinine phosphokinase, ANA-positivity, and elevated thyroid-stimulating hormone (TSH) were more common in this group. The mean fever level was $38.2 \pm 0.7\,^\circ$C and the number of days with fever was 28 ± 24. When fever course was examined, the fever level in NIID patients was lower compared to the other groups especially at week 4 (p = 0.018). In patients diagnosed with NIID, independent risk factors were history of previous disease and arthralgia. Compared to the other groups, the mean leukocyte level was found to elevate significantly more after the third week. The mean CRP level was 64.4 mg/dl in NIID patients. Compared to the other groups the CRP level was found to be higher (p = 0.006). In the NIID group, CRP levels were still higher after the second week, in contrast to the other groups with a lower CRP course.

Undiagnosed (U) group

In 24 of our cases (15.6%) no diagnosis could be established that would explain FUO. The mean age of these cases was 50 ± 17 years, significantly higher than in the other groups (p = 0.028). The mean duration of follow-up in these patients was 40 ± 11 days. The most commonly observed symptoms in the undiagnosed cases were fatigue, weight loss, tachycardia, and cough. The most common physical finding was lymph node enlargement. The mean leukocyte count of the cases was lower compared to the mean counts of diagnosed patients (p = 0.022). Anemia was found in 87% of the undiagnosed patients and it was considerably higher compared to the diagnosed patients (61%) (p = 0.012). Tachycardia, cough, and lymphadenopathy were independent risk factors in the undiagnosed group. In the undiagnosed group, 8% of the cases were <30 years old and 33% were over 60. The corresponding percentages were 35% and 17% (p = 0.007) in the diagnosed group.

Discussion

In most collected FUO series, infection has been the most common diagnosis overall, accounting for 25—50% of cases. Among the infections responsible for FUO, tuberculosis, abscesses, endocarditis, and complicated urinary tract infections have consistently been among the most important.[13,14] The relative frequency by which the major diagnostic categories are represented in series of classic FUO, varies according to both the era in which the series was published and its country of origin;[15] for example, Kikuchi—Fujimoto disease, an unusual form of necrotizing lymphadenitis seen primarily in Japan, and familial Hibernian fever, an inherited periodic fever syndrome described mostly in Ireland.[16,17]

Since the mid-1900s, the frequencies of infections and malignant neoplasms identified as causes of classic FUO have fallen steadily, whereas the proportion of miscellaneous causes and undiagnosed conditions has risen.[18] However, in developing countries, there has been little change in the frequency of diagnosis of infections. Deficient sanitary measures may be important factors in developing countries. Consequently, malignant neoplasms and connective tissue disorders are comparatively less important as causes of classic FUO than in developed countries. In our country, infections have traditionally been the most important causes of FUO.[19]

This is the first prospective and multicenter study in Turkey, although several studies have reported the prevalence and causes of FUO. Infectious diseases have been the leading causes in the etiology of FUO and seem to have been decreasing since the first publication. Tuberculosis, brucellosis, and salmonellosis have decreased as well, while CMV infections have increased possibly due to advancing medicinal services in the management of chronic diseases and underlying pathologies.

When all Turkish FUO studies are taken into account, tuberculosis, which remains one of the deadliest diseases in the world, is still the leading infection among the transmissible causes of FUO in our country (Table 5).[19—26] The same is also valid in this present study in which half of the cases were in the miliary form emphasizing that the disease is

Table 5 Etiologic spectrum of the FUO cases over three periods of study in Turkey

	Year	Total number of cases	Reference No.	ID %	NIID %	MD %	Mi %	U %
First period	1984	70	26	64	10	11	10	4
Second period	1984—2002	491	19—25	50	14	16	5	14
Present study	2004	154		34	31	14	5	16

ID, infectious diseases; NIID, non-infectious inflammatory diseases; MD, malignant diseases; Mi, miscellaneous; U, undiagnosed.

diagnosed in the latter stages. The World Health Organization estimates that each year more than eight million new cases of tuberculosis occur.[27] Ninety-five percent of tuberculosis cases occur in developing countries, where the disease goes undiagnosed due to deficient capabilities.[28] Despite the enormous global burden of the disease and the overall low rates of case detection worldwide, conventional approaches for diagnosis have relied on tests that have major limitations. For example, sputum smear microscopy is insensitive; culture is technically complex and slow; determination of drug susceptibility is even more technically complex and slower yet; chest radiography is non-specific; and tuberculin skin testing is imprecise, and the results are often non-specific.[29] Consequently, owing to insufficient diagnosis when compared with other bacterial infections, tuberculosis frequently falls into the FUO category as in Turkey. In contrast, brucellosis, once reported to be the one of the leading causes of FUO,[24] has declined over the course of time probably due to easier diagnostic capabilities compared with tuberculosis. Thus, infections on the whole have shown a decrease within the FUO etiology in recent years, but the frequency of tuberculosis has not actually declined.

Our review of the literature revealed that the proportion of FUO cases grouped into specific disease categories has changed during the past decades.[19—26] Infections have been the most important causes of FUO in nearly all reports including this study, with a relative frequency ranging from 64% to 50%. Turkish studies, including this one, show that the proportion of infectious diseases has steadily decreased in the past decades, although tuberculosis is the most common infection in our country. This trend may be attributed to the use of rapid diagnostic tests, invasive procedures, and developed imaging techniques all of which can be interpreted with the improving capabilities of the healthcare system. Consequently, infections are diagnosed at earlier stages and prolonged febrile illnesses without established etiologies despite intensive evaluation and diagnostic testing are confined to hard-to-detect transmissible diseases like tuberculosis.

The second greatest cause of FUO was NIID (30.5%) in our trial. Other studies have reported rates around 10—14%.[19—26] Adult Still's disease was found to be the leading etiology of FUO in the group of NIID and comprised approximately 14% of all the cases. In other series, SLE and temporal arteritis have been the most common disorders. Compared to the previous studies, the proportion of NIID has steadily increased. However, the nature of NIID varies in our country. A rapid immunologic diagnosis by using an assay of antinuclear and anti-DNA antibody can be used to diagnose SLE. On the other hand, adult Still's disease is accompanied by high-grade fever and systemic symptoms, and is a common cause of FUO. However, the clinical signs, symptoms, and diagnosis of adult Still's disease are still more complex compared to SLE and temporal arteritis. Despite rich symptoms, signs, and laboratory findings, these are non-specific findings and are usually non-diagnostic. The diagnosis of this disease is usually made following elimination of other diseases that take place in the differential diagnosis. This is the reason for the delay in diagnosing patients with Still's disease and might explain why the proportion of the disease as a cause of FUO has been increasing over time.

The frequency of malignant diseases in our trial, which accounted for 14.3% of FUO, is comparable to that found in previous studies varying between 11.7% and 17%. These similar results suggest that patients with tumors are probably recognized thanks to the widespread use of radioimaging techniques in most Turkish hospitals, and thus the proportion of neoplasms associated with FUO has not changed.

It is difficult to explain why the number of undiagnosed cases remains high in our study. Several possible factors may have played a role. The application of intensive and aggressive medical treatments in the early phases of disease, especially in patients who are referred from primary and secondary healthcare facilities to tertiary hospitals, could be the cause of equivocal clinical and laboratory findings. Higher frequencies of advanced age and anemia in the undiagnosed cases suggest that some of them might be malignant diseases or NIID cases such as temporal arteritis, which could be difficult to diagnose due to limited diagnostic resources.

Among the total tests, positive result rates were low for both immunologic serology and microbiologic serology tests (12.8%, 4.2%). However, the diagnostic significance of these tests among positives was high (40%, 53%). Microbiologic serology tests had a diagnostic significance of 30% in the ID group and immunologic serology tests had a diagnostic significance of 17% in the NIID group.

CRP is one of the acute phase reactants. Contrary to expectations, in our ID cases, CRP levels were not high compared to other groups. Decreasing CRP levels in the ID group started from the first week and a lack of substantial change during the subsequent days may be associated with antibiotic use. CRP levels remained quite high in the NIID group at weeks one and four. The decrease in CRP levels in our cases during the second and third weeks and its fluctuated course might be associated with disease activation or medications used. Leukocyte values were higher in the ID and MD groups compared to the other groups. These elevated levels were more striking especially in the MD group during the first four weeks compared to the ID group. These elevations were significant in the NIID group especially after the second week and remained high compared to other groups.

For imaging techniques, our possibility of obtaining positive results was high and these techniques had a diagnostic value in only a quarter of cases with positive findings. These results suggest that positive findings obtained by imaging

techniques have a low rate of contribution to FUO etiology. Nonetheless, when all groups were evaluated, it was seen that imaging methods had diagnostic value in a substantial percentage of MD (54%) and ID (47%) cases, and they were indispensable diagnostic methods for monitoring FUO cases. Our study results show that imaging techniques made a small contribution to the diagnosis in the NIID group (11%).

The FUO definitions include epidemiological controversies.[30] Evolving from a one-week stay in hospital to three outpatient visits or three days of hospital stay as suggested by Durack and Street has made the definition even more biased. Pre-hospital healthcare facilities vary between countries, and even within a country depending on the referral system.[31] Our study results demonstrate that the mean time to definite diagnosis in all of our cases was 32 ± 18 days and this suggests that the Petersdorf and Beeson criteria should still be applicable for FUO identification in developing countries such as Turkey.

In conclusion, the spectrum of diseases causing FUO in Turkey continues to change. Infection remains the most common cause and the high percentage of cases with tuberculosis points to the fact that we should be aware of tuberculosis as a likely cause of FUO. The proportion of NIID has been increasing, possibly due to improving living conditions throughout the country by reducing the proportion of infections. However, further studies conducted in different geographic locations with prospective and multicenter designs are needed to track the changing etiology of FUO and facilitate its early diagnosis and appropriate management.

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