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Original Article

Clinico-epidemiological profile of fever of unknown origin in an Egyptian setting: A hospital-based study (2009–2010)

Ahmed F Kabapy[1,2], Amira M Kotkat[1], Hanan Z Shatat[1], Ekram W Abd El-Wahab[1]

[1] *Tropical Health Department, High Institute of Public Health, Alexandria University, Egypt*
[2] *Alexandria Fever Hospital, Alexandria, Egypt*

Abstract

Introduction: Fever of unknown origin (FUO) is one of the most challenging diagnostic dilemmas in the field of infectious diseases and tropical medicine. Clinicians should use the frequency distribution of disorders causing FUO to guide their diagnostic approach in patients with prolonged, unexplained fevers meeting the definition of FUO.

Methodology: The present study was undertaken to examine the etiologies, clinico-epidemiologic profile, and prognosis of classical FUO in patients reporting to the Alexandria Fever Hospital in Egypt. Records of 979 patients admitted to the fever hospital (from January 2009 to January 2010) and diagnosed as having FUO were examined carefully. FUO was defined as three outpatient visits or three days in the hospital without elucidation of cause of fever.

Results: A total of 979 cases (57.0% males and 43.0% females), with ages ranging from 0.2 to 90 years, were investigated. The mean duration of fever before hospitalization was 31 ± 10 days. The etiology of FUO was delineated in 97% of cases, and only 3% remained undiagnosed. Diagnoses were grouped into five major categories. Infectious causes of FUO were strongly associated with better outcome (73.7% improved). Smoking, contact with animals or birds, drug addiction, and HIV seropositivity were important risk factors associated with infections.

Conclusions: Infections are the most common cause of FUO, followed by collagen vascular diseases, in our region. A three-step diagnostic work-up approach is recommended to be applied in Egypt in order to improve the quality of medical service provided to FUO patients.

Key words: fever of unknown origin; classical; infectious diseases; collagen vascular diseases.

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Introduction

Fever of unknown origin (FUO) is one of the most challenging diagnostic dilemmas in the field of infectious diseases and tropical medicine. Fever is a cardinal manifestation of many disorders, including both infectious and non-infectious diseases [1].

There are two definitions for FUO. The old definition was provided by Petersdorf and Beeson in 1961 and is a temperature higher than 38.3°C on several occasions and lasting longer than three weeks, with a diagnosis that remains uncertain after one week of investigation [2]. Different definitions have been put forward to describe the difference in the length of a diagnostic work-up, taking into account the outpatient setting. This has now been modified to include patients who are undiagnosed after two outpatient visits or three days in the hospital [3]. Durack *et al*. have argued for a more comprehensive definition of FUO that takes into account medical advances and changes in disease states, such as the emergence of human immunodeficiency virus (HIV) infection and an increasing number of patients with neutropenia [4]. The new definition proposed, in addition to the old definition criteria, to include patients who are undiagnosed after two outpatient visits within one week or have spent three days in hospital. Some authors suggested that FUO at the present time should signify prolonged fevers with temperatures of at least 38.3°C, which remain undiagnosed after a focused and appropriate laboratory work-up [3,5]. This clinical definition is useful and eliminates two of the major diagnostic problems in using the expression FUO as a diagnostic term. Many clinicians diagnose patients with FUO who have had an inadequate laboratory work-up or who have not had prolonged, undiagnosed fevers for three or more weeks [3,5,6]. The diagnostic work-up should be focused and based on the clues provided by the patient's history, physical exam, and laboratory tests that suggest an organ system involvement or category

of disorder causing the FUO, such as collagen vascular disease, malignancy, infections, *etc*. It makes little sense to order tests for every conceivable cause of an FUO when there is nothing to suggest the diagnosis [7-10].

Clinicians should use the frequency distribution of disorders causing FUO to guide their diagnostic approach in patients with prolonged, unexplained fevers meeting the definition of FUO [6]. Disorders presenting as FUO are varied and extensive. Clinicians often order every conceivable test to try to diagnose all of the myriad causes of FUO that are part of the differential diagnosis of FUO in general, but are not sign and symptom related [11]. The greatest errors in FUO work-up relating to the diagnostic evaluation are related to over testing and under testing. Ordering tests that have no potential clinical usefulness is wasteful and unnecessary. Alternately, few diagnostic tests, particularly those that are necessary and appropriate, are not relevant to the clinical setting and prolong a misdirected diagnostic FUO work-up. The key to the diagnostic approach with FUOs is a focused and complete clinically relevant work-up. Using a focused approach, physicians can arrive at a definitive diagnosis more quickly, less expensively, and less invasively than using the "shotgun" approach [11]. Many simple diagnostic tests such as erythrocyte sedimentation rate (ESR) may help to separate benign from more serious entities, thus steering the clinician to a specific path [12].

Nowadays, because of the tremendous advances in pharmaceutics, the numbers of medications patients take make the diagnosis of drug fever as a cause of FUO relatively more common. In addition, the relative incidence of malignancy increases with age, and this is reflected in the series on FUOs [13]. Recent advances in imaging techniques allow non-invasive diagnosis of many diseases – for example, diagnosis of subacute bacterial endocarditis by echocardiography, and diagnosis of obscure intra-abdominal abscesses, masses, and tumors by computerized tomography (CT) and magnetic resonance imaging (MRI) [14].

The present study was undertaken to look at the etiologies, clinico-epidemiologic profiles, and outcomes of classical FUO in patients reporting to the Fever Hospital in Alexandria province in Egypt. The study of FUO and its relation to diseases will improve the fast diagnosis of patients and will prevent the discriminate use of antibiotics in developing countries.

Methodology

A retrospective, descriptive, epidemiological study was conducted at Alexandria Fever Hospital, Egypt. Both old and new definitions of FUO were applied for enrolled cases. Prior to starting the work, a pilot study was conducted on a small subset of patients (n = 20) in order to obtain information that may improve the research plan and facilitate the execution of the study. Records of a total of 979 admitted cases in the years 2009–2010 were carefully reviewed. Predesigned data collection sheets were used to collect data about patients' demographics and medical data that included complete history of the present complaints, number of febrile days before and during hospitalization, fever pattern from the temperature chart, admission and discharge dates, associated medical conditions, basic investigations requested, empirical treatment given to the patient, final diagnosis, discharge type, and outcome.

Statistical analysis

Data were collected, revised, coded, and entered into the computer. Statistical analysis was performed using the Statistical Package for Social Sciences version 18.0. Significance of the obtained results was judged at the 5% level of significance. Descriptive statistics such as frequency distribution, mean, median, standard deviation, and interquartile range were used to describe selected variables of the studied population. Bivariate analysis, odds ratio with confidence interval of 95%, Pearson's Chi-squared test, Monte Carlo test, and Fisher's exact test of significance were used, when applicable, for testing statistical association, with a p value less than 0.05 taken to mean statistical significance.

Ethics statement

The study was approved by the institutional review board and the ethics committee of the High Institute of Public Health affiliated with Alexandria University, Egypt, as well as the Central Directorate for Research and Health Development in the Ministry of Health. The research was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Data sheets were coded to ensure anonymity and confidentiality of patients' data.

Results

Old versus new FUO definition

The total number of enrolled cases (979), which included cases that satisfied both the old [2] and the new [4,6] definitions of FUO, was reduced to 555 cases when only the old definition was applied. Accordingly, half of the patients (49.54%) were diagnosed with bronchitis. The diagnoses were grouped into five major categories: infectious diseases (63.4%), autoimmune diseases (30.3%), malignancies (0.9%), miscellaneous conditions (2.2%), and defied diagnosis (3.2%) (Table 1). This affected the distribution of major diagnostic categories in favor of infectious diseases. In the light of this, this study focused only on the cases that were compliant with the old definition (n = 555) throughout the rest of the study results.

Figure 1. Presenting complaints among FUO cases

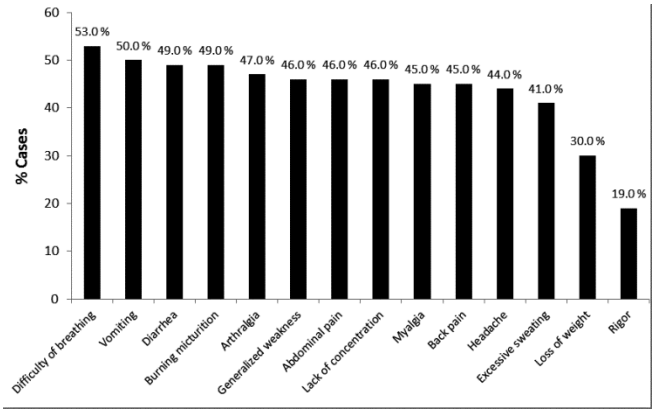


Table 1. Final diagnosis according to old versus new definition of fever of unknown origin (FUO)

	New definition (N= 979)	Old definition (N = 555)
	N (%)	N (%)
Autoimmune diseases	**170 (17.4)**	**168 (30.0)**
Systemic lupus	63 (6.4)	63 (11.4)
Rheumatoid arthritis	45 (4.6)	45 (8.1)
Rheumatic fever	44 (4.5)	42 (7.6)
Autoimmune hepatitis	16 (1.6)	16 (2.9)
Behcet disease	2 (0.2)	2 (0.4)
Infectious diseases	**774 (79.1)**	**352 (63.4)**
Bronchitis	485 (49.5)	65 (11.7)
Bronchopneumonia	25 (2.6)	25 (4.5)
H1N1 influenza	1 (0.1)	1 (0.2)
Pneumonia	21 (2.2)	21 (3.8)
Tuberculosis	11 (1.1)	11 (2.0)
Urinary tract infection	103 (10.5)	101 (18.2)
Brucella	42 (4.3)	42 (7.6)
Typhoid fever	28 (2.9)	28 (5.0)
Fasciola	2 (0.2)	2 (0.4)
Leptospira	4 (0.4)	4 (0.7)
Chicken pox	2 (0.2)	2 (0.4)
German measles	1 (0.1)	1 (0.2)
Cytomegalovirus	3 (0.3)	3 (0.5)
Gastroenteritis	7 (0.7)	7 (1.3)
Hepatitis A virus	1 (0.1)	1 (0.2)
Hepatitis B virus	1 (0.1)	1 (0.2)
Hepatitis C virus	22 (0.3)	22 (4.0)
Encephalitis/meningitis	8 (0.8)	8 (1.4)
Sepsis	7 (0.7)	7 (1.3)
Malignancy	**5 (0.5)**	**5 (0.9)**
Tumor (unspecified)	4 (0.4)	4 (0.7)
Pancreatic tumor and obstructive jaundice	1 (0.1)	1 (0.2)
Miscellaneous	**12 (1.2)**	**12 (2.2)**
Hyperthyroidism	9 (0.9)	9 (1.6)
Glomerulonephritis and renal failure	3 (0.3)	3 (0.5)
Undiagnosed	**18 (1.8)**	**18 (3.2)**

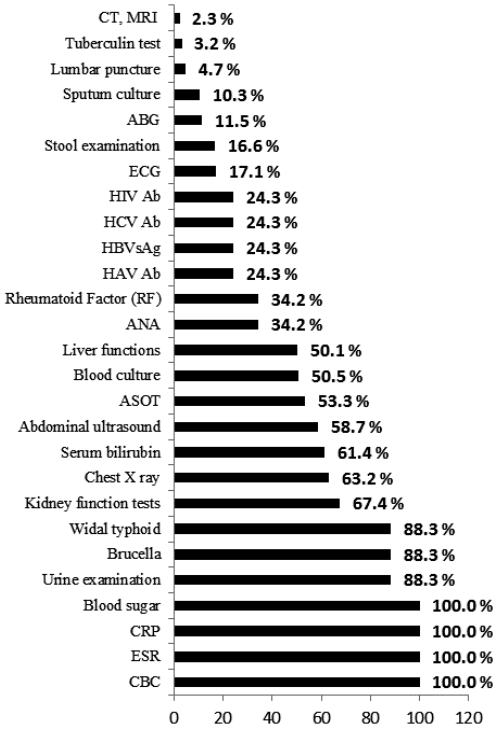
Sociodemographic characteristics of the patients

The ages of the study population ranged from 2 months to 90 years, with a mean age of 32 years. About 57% of the study population were males and 43% were females, with a 1.3:1 male-to-female ratio. About 11% of the studied females were pregnant. Other demographic criteria are detailed in Table 2.

Clinical features, management, and outcome of FUO

Patients mostly presented with non-specific constitutional symptoms (Figure 1). The febrile period before admission ranged from 21 days up to 50 days (mean ± standard deviation [SD] = 31 ± 10 days). In almost half of the cases (48%), the febrile period was three to four weeks (48%). The pattern of fever was either continuous (48%), continuous with abrupt onset and remission (45.2%), or remittent (6.8%). The most common clinical findings on clinical examination were drowsiness (50.5%), congested throat (51.0%), coated tongue (50.5%), cervical lymphadenopathy (48.6%), tachycardia (33.0%), tachypnea and abnormal air entry (15%), joint inflammation (14.2%), cyanosis (13.0%), and rash (9.9%). Details about other clinical features of the admitted cases are listed in (Table 3).. Half of the cases (49.9%) were hospitalized for a period less than one week, and only 0.40% required hospitalization for four to five weeks. The mean duration of hospitalization was 7 ± 4 days and ranged from 1 to 31 days.

Figure 2. Basic investigations done for admitted cases with FUO



CBC: complete blood count, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, ASOT: anti streptolysin O titer, ANA: antinuclear anti body, HAV Ab: hepatitis A virus antibody, HBVsAg: hepatitis B surface antigen, HCV Ab: hepatitis A virus antibody, HIV Ab: human immunodeficiency virus antibody, ECG: electrocardiogram, ABG: arterial blood gases, CT: **computerized tomography,** MRI: magnetic resonance imaging

Table 2. Sociodemographic criteria of FUO cases

Demographic criteria	**N (%)**
Age	
< 10	92 (16.6)
10–19	77 (13.9)
20–29	167 (30.1)
40–59	150 (27)
60– 90	69 (12.4)
Gender	
Male	316 (56.9)
Female	239 (43.1)
Pregnant	26 (10.9)
Occupation	
Not working	255 (45.9)
Children and students	138 (24.9)
Manual worker	125 (22.5)
Office employee	31 (5.6)
Military personnel	6 (1.1)
Residence	
Rural	117 (21.1)
Urban	438 (78.9)
Marital status	
Single	186 (33.5)
Married	188 (33.9)
Unmarried & underage	181 (32.6)

Table 3. Clinical features of FUO cases

Clinical features	N	%
General look		
Normal	62	11.2
Ill	407	73.3
Toxic	86	15.5
Consciousness		
Normal	266	47.9
Drowsy	281	50.6
Semiconscious	2	0.4
Comatose	6	1.1
General examination		
Cyanosis	75	13.5
Lower limb edema	63	11.4
Joints findings	79	14.2
Rash	55	9.9
Icteric sclera	29	5.2
Clubbing	16	2.9
Vital signs		
Hypotensive	33	6
Hypertensive	100	18
Tachypnea for age (mean ± SD = 92 ± 22)	83	15
Tachycardia for age (mean pulse = 92 ± 22 b/min)	183	33
Fever (> 37.5°C), (mean ± SD = 39 ± 1)	384	69
Hyperpyrexia (> 40)	171	31
Fever pattern		
Continuous	266	47.9
Continuous with abrupt onset and remission	251	45.2
Remittent	38	6.8
Febrile period before admission (weeks)		
3 weeks	271	48.8
4 weeks	88	15.9
5 weeks	84	15.1
6 weeks	91	16.4
7–8 weeks	21	3.8
(Range = 21–50, mean = 31 ± 10 days)		
Head and neck		
Coated tongue	280	50.5
Congested throat and tonsils	283	51
Enlarged cervical lymph nodes	270	48.6
Chest examination		
Abnormal air entry	87	15.7
Rhonchi or crepitation	48	8.6
Wheezes	40	7.2
Hemoptysis	36	6.5
Heart examination		
Abnormal heart sounds	3	0.5
Murmurs	12	2.2
Diastolic	3	25
Systolic	9	75
Abdominal examination		
Distended abdomen	36	6.5
Scared abdominal wall	129	23.2
Enlarged liver	26	4.7
Enlarged spleen	22	4
Ascites	21	3.8

Table 3 (*continued*). Clinical features of FUO cases

Clinical features	N	%
Nervous system examination		
Neck rigidity	8	1.4
Kerning sign	8	1.4
Brudzinsky sign	8	1.4
Abnormal reflexes	8	1.4
Abnormal peripheral sensations	133	24
Weak motor power	8	1.4
Abnormal psychological status	9	1.6
Co-morbidities		
Diabetes mellitus	133	24
Hypertension	72	13
Heart disease	58	10.5
Bronchial asthma	54	9.7
Chronic obstructive pulmonary disease	51	9.2
Allergy	45	8.1
Rheumatic disease	30	5.4
Malignancy	16	2.9
Hepatitis C virus	11	2
Human immunodeficiency virus	8	1.4
Hepatitis B virus	1	0.2
Risky behaviors and exposures		
Smoking	118	21.3
Drug abuse	50	9
Travelling abroad	2	0.4
Contact with animals	44	7.9
Contact with birds	41	7.4

SD: standard deviation

Figure 3. Discharge type and outcome among FUO cases

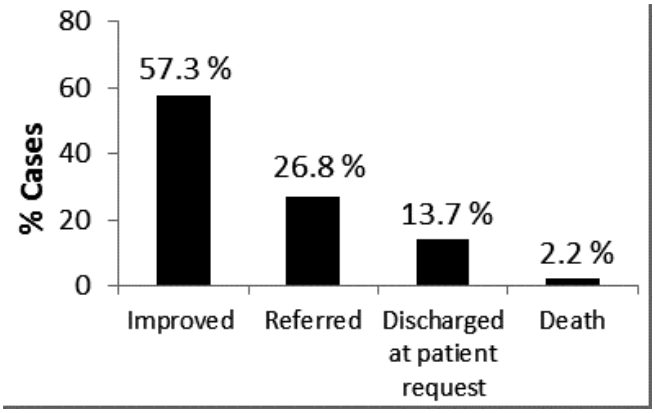
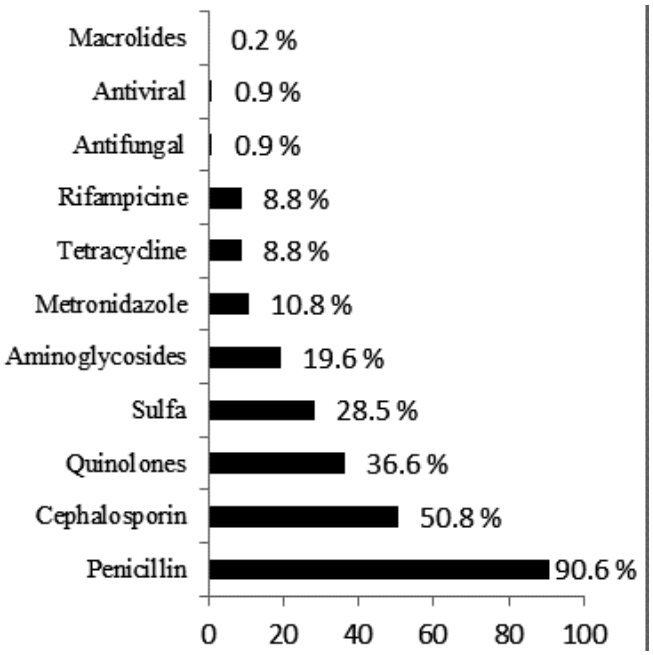


Figure 4. Treatment with antimicrobial group among FUO cases



Initial routine and more specific investigations were done to reach a final decision about the diagnosis (Figure 2). Diagnosis of FUO was achieved in 97% (n = 537) of cases, whereas only 3% of cases (n = 18) remained undiagnosed. Infectious diseases were the predominant causes of FUO among special groups: those under 10 years of age (65.0%), over 60 years of age (62.0%), pregnant females (76.9%), and drug abusers (78.0%) (Table 4). Empirical antimicrobials, mainly penicillin (91.6%), cephalosporin (50.8%), quinolone (36.6%), sulfa (28.5%), and aminoglycosides (19.6%) were given for treatment (Figure 3). About 57.3% of the cases improved, whereas 2.2% died (Figure 4). Infectious causes of FUO were strongly associated with better outcome (73.7% improved, $p < 0.0001$) (Table 5).

Risk estimation for different FUO causes

Analysis of risk showed that it was more likely for FUO cases to have an infectious disease if the patient was a smoker, drug addict, HIV positive or had had contact with animals or birds. Furthermore, it was more likely for FUO cases to have an autoimmune disease if the patient was a female (Table 6).

Table 4. Final diagnosis in special groups of enrolled FUO cases

Diagnosis	Under 10 (n = 92)	Over 60 (n = 69)	Pregnant (n = 26)	Drug abusers (n = 50)
	N (%)	N (%)	N (%)	N (%)
Infectious diseases	**60 (65.0)**	**43 (62.0)**	**20 (76.9)**	**39 (78.0)**
Bronchitis	28 (30.4)	2 (3.0)	1 (3.8)	8 (16.0)
Brucella	6 (7.0)	0 (0.0)	2 (7.7)	8 (16.0)
Urinary tract infection	6 (7.0)	16 (23.0)	11 (42.3)	7 (17.0)
Broncho-pneumonia	4 (4.3)	9 (13.0)	0 (0.0)	4 (8.0)
Encephalitis/meningitis	4 (4.3)	0 (0.0)	1 (3.8)	4 (8.0)
Gastroenteritis	4 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	3 (3.2)	2 (3.0)	0 (0.0)	4 (8.0)
Typhoid fever	2 (2.1)	3 (4.0)	3 (11.5)	1 (2.0)
Chicken pox	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cytomegalovirus	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
German measles	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis C virus	0 (0.0)	5 (7.0)	1 (3.8)	4 (8.0)
Fasciola	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)
Leptospira	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Tuberculosis	0 (0.0)	1 (1.0)	0 (0.0)	3 (6.0)
Autoimmune diseases	**28 (31.0)**	**19 (27.5)**	**6 (23.1)**	**2 (4.0)**
Rheumatic fever	18 (20.0)	0 (0.0)	1 (3.8)	0 (0.0)
Systemic lupus erythematosus	10 (11.0)	7 (10.0)	5 (19.2)	0 (0.0)
Rheumatoid arthritis	0 (0.0)	9 (13.0)	0 (0.0)	1 (2.0)
Autoimmune hepatitis	0 (0.0)	3 (4.0)	0 (0.0)	1 (2.0)
Malignancy	**0 (0.0)**	**2 (3.0)**	**0 (0.0)**	**1 (2.0)**
Undiagnosed	**4 (4.3)**	**2 (3.0)**	**0 (0.0)**	**4 (8.0)**
Other	**0 (0.0)**	**3 (4.0)**	**0 (0.0)**	**4 (8.0)**

Table 5. Correlation between the final diagnosis and common demographic and medical features of the patients

	Infectious diseases	Autoimmune diseases	Malignancy	Un-diagnosed	Miscellaneous	P value
	N (%)	N (%)	N (%)	N (%)	N (%)	
Age						
<10	60 (17.0)	28 (16.7)	0 (0.0)	4 (22.2)	0 (0.0)	
10–19	44 (12.5)	29 (17.3)	0 (0.0)	3 (16.7)	1 (8.3)	
20–39	110 (31.2)	50 (29.8)	0 (0.0)	4 (22.2)	3 (25.0)	0.43
40–59	95 (27.0)	42 (25.0)	3 (60.0)	5 (27.8)	5 (41.7)	
60–90	43 (12.2)	19 (11.3)	2 (40.0)	2 (11.1)	3 (25.0)	
Gender						
Male	193 (61.1)	98 (31.1)	4 (1.3)	9 (2.8)	12 (3.8)	**0.021**
Female	159 (66.5)	70 (29.3)	1 (0.4)	9 (3.8)	0 (0.0)	
Pregnant	20 (76.9)	6 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.449
Drug abuser	39 (78.0)	2 (4.0)	1 (2.0)	4 (8.0)	4 (8.0)	**0.001**
Residence						
Rural	66 (56.4)	42 (35.9)	1 (0.9)	4 (3.4)	4 (3.4)	0.342
Urban	286 (65.3)	126 (29.8)	4 (0.9)	14 (3.2)	8 (1.8)	
Occupation						
Manual worker	81 (64.8)	36 (28.8)	0 (0.0)	3 (2.4)	5 (4.0)	
Military	4 (66.7)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Children	87 (63.0)	45 (32.6)	0 (0.0)	6 (4.3)	0 (0.0)	**0.051**
Not working	164 (64.3)	77 (30.2)	3 (1.2)	7 (2.7)	4 (1.6)	
Desk employee	16 (51.6)	8 (25.8)	2 (6.5)	2 (6.5)	3 (9.7)	
Period in the hospital						
< 1 week	154 (44.0)	103 (61.0)	3 (60.0)	10 (55.0)	7 (58.0)	
1 week	155 (44.0)	55 (33.0)	2 (40.0)	7 (39.0)	4 (33.0)	**0.038**
2–5 weeks	43 (12.0)	10 (6.0)	0 (0.0)	1 (6.0)	1 (8.0)	
Febrile Period						
3 weeks	177 (50.3)	75 (44.6)	1 (20.0)	11 (61.1)	7 (58.3)	
4 weeks	57 (16.2)	24 (14.3)	1 (20.0)	3 (16.7)	3 (25.0)	
5 weeks	53 (15.1)	27 (16.1)	2 (40.0)	2 (11.1)	0 (0.0)	0.368
6 weeks	52 (14.8)	36 (21.4)	1 (20.0)	0 (0.0)	2 (16.7)	
7–8 weeks	13 (3.7)	6 (3.6)	0 (0.0)	2 (11.1)	0 (0.0)	
Fever pattern						
Continuous	175 (50.0)	78 (46.0)	1 (20.0)	5 (28.0)	7 (58.0)	
Continuous with abrupt remission	154 (43.0)	78 (46.0)	3 (60.0)	12 (66.0)	4 (33.0)	0.516
Remittent	23 (7.0)	12 (7.0)	1 (20.0)	1 (6.0)	1 (8.0)	
Discharge type & outcome						
Improved	98 (73.7)	33 (24.8)	1 (0.8)	0 (0.0)	1 (0.8)	
Discharged at request of patient	0 (0.0)	4 (50.0)	0 (0.0)	3 (37.5)	1 (12.5)	**0.00**
Referred	25 (53.2)	19 (40.4)	1 (2.1)	2 (4.3)	0 (0.0)	
Died	31 (34.8)	47 (52.8)	1 (1.1)	5 (5.6)	5 (5.6)	

Table 6. Risk estimation for different diagnostic categories

Variable	Infectious diseases			Autoimmune diseases			Malignancy		
	OR	95% CI		OR	95% CI		OR	95% CI	
		LL	UL		LL	UL		LL	UL
Gender (male/female)	1.27	0.89	1.8	**0.92**	**0.64**	**0.97**	0.33	0.04	2.95
Residence (rural/urban)	1.45	0.96	2.2	0.72	0.47	1.11	1.07	0.12	9.66
Unemployed	0.93	0.66	1.32	1.01	0.7	1.45	0.56	0.09	3.4
Child	1.02	0.69	1.52	0.87	0.57	1.31	-		
Manual worker	0.93	0.61	1.4	1.1	0.71	1.7	-		
Desk employee	1.68	0.81	3.47	1.26	0.55	2.89	0.08	0.01	1.52
Military	0.87	0.16	4.77	0.87	0.16	4.78	-		
Married	1.01	0.7	1.45	1.26	0.85	1.86	0.34	0.06	2.04
Age category under 10	0.91	0.57	1.46	0.99	0.61	1.61	-		
Age category 10–19	1.36	0.83	2.22	0.68	0.41	1.12	-		
Age category 20–39	0.86	0.59	1.26	1.02	0.69	1.52	-		
Age category 40–59	1.01	0.68	1.48	1.16	0.77	1.76	0.24	0.04	1.47
Age category 60–90	1.06	0.63	1.78	1.16	0.66	2.04	0.21	0.03	1.27
Pregnancy	0.51	0.2	1.28	1.47	0.58	3.73	-		
Smoking	**1.37**	**1.2**	**2.07**	0.94	0.6	1.45	1.08	0.12	9.76
Drug abuse or addiction	**1.46**	**1.23**	**3.92**	11.8	0.82	48.9	0.39	0.04	3.57
Travelling abroad	1.74	0.11	27.9	0.43	0.03	6.96	-		
History of jaundice	0.03	0.0	0.23	-			0.38	0.04	3.49
Contact with animals	**1.66**	**1.55**	**1.78**	-			-		
Contact with birds	**1.65**	**1.54**	**1.77**	-			-		
History of operations	1.08	0.72	1.63	0.87	0.57	1.33	0.45	0.07	2.73
Diabetes mellitus	0.97	0.65	1.46	1.17	0.76	1.8	0.21	0.03	1.25
Heart disease	0.76	0.42	1.36	1.41	0.75	2.65	0.17	0.03	1.04
Hypertension	0.45	0.25	0.81	**2.39**	**1.25**	**4.56**	0.59	0.07	5.38
Bronchial asthma	1.12	0.63	1.99	0.86	0.47	1.55	-		
Chronic obstructive pulmonary disease	0.94	0.52	1.72	1.3	0.67	2.51	0.15	0.02	0.9
Hepatitis C virus	0.17	0.02	1.33	4.43	0.56	34.9	-		
Hepatitis B virus	-			-			-		
Rheumatic disease	1.35	0.64	2.84	N/A			0.22	0.02	2.06
Human immunodeficiency virus	**1.57**	**1.12**	**2.87**	1.31	0.26	6.54	-		
Malignancy	1.04	0.37	2.91	1.31	0.42	4.13	N/A		
Allergy	1.3	0.7	2.4	0.63	0.33	1.17	-		

-: Could not be calculated; OR: odds ratio; CI: confidence interval; LL: lower limit; UL: upper limit

Discussion

Applying the new definition of FUO has resulted in misdiagnosis of a significant portion of the cases. Almost half were diagnosed with bronchitis, which was reflected in the distribution of final diagnosis in favor of infectious diseases. One drawback of the new definition is that it does not set a minimal required list of laboratory and imaging tests after which the patient is diagnosed with FUO. This leaves the matter to the judgment of the physician and thus creates bias. Some studies adopted the old definition, which set the criteria of diagnosis to fever for more than three weeks without apparent diagnosis [6,15]. Others adopted the new FUO definition, which included patients who remained undiagnosed after two outpatient visits, regardless of the duration of fever [16,17]. Middle-aged patients were the most represented among FUO cases, with no sex predilection; these results are in line with the demographic composition of Egypt, where a major proportion of the population is children. The mean age varied in other studies conducted in Iran and Netherlands (30 versus 49.2 [18] and 53 years [19], respectively). It was difficult to correlate textbook definitions of reported fever patterns among the study population to specific diseases. This was attributed to the use of antipyretics before hospitalization and after hospitalization, as it is not ethical to keep a patient in high fever just for the sake of recording the temperature charts, which usually takes a few days.

Lack of facilities and services may be behind the short hospitalization period compared to other studies. Two weeks is a short time to reach an appropriate diagnosis and treatment. Some patients were discharged on their request. The high empirical use of penicillin reflects the provisional diagnosis of most of FUO cases as infections. This raises issues such as drug-resistant bacteria, drug tolerance by patients, and wasting precious resources in useless endeavors. Clinicians in many situations are forced by the patients to help relieve the presenting condition. In light of the current situation of the healthcare system in Egypt, patients do not have enough time and resources to help the attending physician reach a definite diagnosis [20].

This study was conducted in the Fever Hospital in Alexandria, a governmental hospital with limited resources. Due to high costs, no specific investigational flow protocol is followed for the diagnosis of FUO in Egypt. Initial investigations are done, which, together with the history and clinical findings, may guide the diagnosis. For example, for those diagnosed with bronchopneumonia/pneumonia, no bacteriological/virological cultures were done to isolate the causative agent, and no antimicrobial sensitivity tests were done where empirical antibiotics were given instead. The diagnosis of non-infectious inflammatory / autoimmune diseases was mainly by Anti Nuclear Antibody and Rheumatoid Factor (ANARF), whereas in other studies, ANCA, Anti Ds-DNA, Anti-Ro and Anti-La were used to reach a more specific diagnosis [21]. In France [16], the diagnostic work-up is split into multiple steps. The first step includes initial hematological biochemical tests such as ESR, C-reactive protein (CRP), complete blood count (CBC), renal and hepatic function tests and electrolytes, creatine phosphokinase, lactate dehydrogenase, ferritin, serum electrophoresis, antinuclear antibodies, rheumatoid factors, microscopic urinalysis, blood and urine cultures, chest radiography, and abdominal and pelvic ultrasonography. The second involves more specific radiological and serological microbiological tests. In the third step, more expensive or invasive tests are used, such as bone marrow aspiration and/or biopsy, liver biopsy, molecular genetic tools, scintigraphy, or positron emission tomography (PET). In Taiwan [21], diagnostic work-up begins with routine hematological and biochemical and radiological investigations performed on all patients. Phase 1 diagnostic protocol is adopted in patients without potential diagnostic clues (PDCs) or with misleading clues, and a phase 2 diagnostic protocol for patients without PDCs is applied when phase 1 did not reveal any. In Saudi Arabia [22], a single diagnostic work-up is done for all cases of FUO that involve most of the above-mentioned investigations. This variability in diagnostic work-up shows the lack of unified approach and guidelines to handle the cases of FUO.

In agreement with other studies [15,16,18,19,23], infection was the most common cause of FUO followed by collagen vascular disease, confirming the trends found in other parts of the world [16,18,19,23]. There is an increased prevalence of connective tissue diseases presented with prolonged unexplained fever [24]. The percentage of cases that remained undiagnosed was much lower than the global rates, even those reported in other studies in developed countries (3% versus 50% [19], 27% [15], 25.7% [16], 16.7% [18], and 13% [23]). This could be attributed to availability of diagnostic tools and financial resources to reach a convincing final diagnosis. Most likely, many cases were misdiagnosed as infectious diseases, and no definitive diagnoses were reached. Physicians may be rushed to reach a probable final diagnosis even if it is inaccurate and may be unsupported by

laboratory investigations and imaging techniques. Patients usually improve with symptomatic treatment, and get discharged as cured cases [25]. The underlying cause of infectious – autoimmune and neoplastic diseases – did not differ substantially from those reported in similar studies conducted in Egypt [23] or other surveyed countries [15,16,18,19]. Nevertheless, a significant number of FUO cases (more than one half) were diagnosed with respiratory tract infections. This may be attributed to a problem with the antimicrobial group used with these patients, as the majority of the patients were cured just by switching to a more appropriate antimicrobial group. Compliance of the patients to the antimicrobial treatment raises other questions about the warranty of antimicrobial drug usage as over-the-counter medication in Egypt [26].

Risk factors are important and help physicians reach a diagnosis of FUO [6]. Some authors identified smoking and added previous use of antibiotics as risk factors for infectious diseases [6,16,17]. In addition to smoking, the present study identified contact with animals or birds, drug addiction, and HIV seropositivity as important risk factors for acquiring infections. Rates of infection were also higher among diabetics and pregnant females. For most autoimmune diseases, there is a clear sex difference in prevalence; females are generally more frequently affected than males [27], and this was evident in the present study. Females have increased immune reactivity, and this greater immunocompetence may translate to greater resistance to infectious and some non-infectious diseases. However, it is possible that this greater immune reactivity makes women more prone to developing autoimmune diseases [27]. Considerations of female gender should be at the forefront of all differential diagnosis of FUO cases. However, as a physician may be more likely to suspect the presence of an autoimmune condition in females more so than in males, this may result in many males remaining undiagnosed [28].

Conclusions

Infections remain the main group of diseases in the evaluation of FUO. The present study infers that malignancy and collagen vascular diseases also comprise the second big group of FUO. In order to improve the quality of medical service provided to FUO patients, and based on a literature review [16,21], a three-step diagnostic work-up approach is recommended.

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Corresponding author

Ekram W. Abd El-Wahab
Tropical Health Department, High Institute of Public Health, Alexandria University
165 El Horreya Road
21561 Alexandria, Egypt
Phone: 00201110456072
Email: ekramwassim@mail.com

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