A retrospective analysis of 3 156 admissions with fever of unknown origin in a large Italian hospital

Nicola Nicolotti[(1)], Caterina Cattel[(2)], Maria Rosaria Gualano[(3)], Alessandra Soriano[(4)], Raffaele Manna[(4)], Stefania Boccia[(5, 6)]

ABSTRACT

BACKGROUND: fever of unknown origin (FUO) is defined as a fever with no etiologic diagnosis after standardized investigations performed during 3 days in hospital or after at least 3 ambulatory visits. Our study aims to describe the epidemiology of classic FUO through the retrospective analysis of 902 861 admissions to a large University Hospital in Italy, to investigate its temporal trend, and to evaluate differences between young and old patients.

METHODS: we retrieved data records of all the admissions between the 1st January 1988 and 31st December 2007. Proportional admission rate (PAR) of FUO was calculated. Time trends of FUO admissions were analysed by joinpoint regression, with time changes expressed as Expected Annual Percent Change (EAPC). The ICD9-CM code was used to identify the diagnosis on discharge of FUO cases.

RESULTS: in the study period 3 156 patients were admitted with a diagnosis of FUO (PAR=3.50 per 1 000). The time-trend analysis showed two joinpoints, the first in 1995 (EAPC of 307.80, 95% CI: 89.66-776.84, p=0.002), and the second in 1998 (EAPC=-8.57, 95% CI: -10.37-6.73; $p<0.001$). Around 22% of admissions remained without a definitive diagnosis of FUO, with this percentage being lower in patients ≥65 years compared with subjects aged 21-64.

CONCLUSIONS: FUO is a leading cause of admission to hospitals, as well as of morbidity and mortality, thus representing a challenge for diagnostic medicine and hospital care. It is necessary to develop a diagnostic methodology for FUO, so as to reduce costs of preventable hospitalizations.

Key words: Fever of unknown origin; Epidemiology; Hospitals; Trends

(1) Department of Epidemiology and Preclinical Research, L. Spallanzani, National Institute for Infectious Diseases (INMI), Rome, Italy
(2) Institute of Geriatrics, Università Cattolica del Sacro Cuore, Rome, Italy
(3) Department of Public Health, University of Turin, Turin, Italy
(4) Department of Internal Medicine-Periodic Fever Research Centre, Università Cattolica del Sacro Cuore, Rome, Italy
(5) Section of Hygiene - Institute of Public Health, Università Cattolica del Sacro Cuore, Rome, Italy
(6) San Raffaele Pisana - IRCCS, Rome, Italy

CORRESPONDING AUTHOR: Maria Rosaria Gualano, Department of Public Health, University of Turin.
Tel: +39 011 6705809; Fax: +39 011 6705889.
e-mail: mar.guala@gmail.com
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INTRODUCTION

Fever of unknown origin (FUO) was defined for the first time in 1961, as a condition including the following symptoms contemporarily: 1) a fever lasting three weeks at least, 2) a temperature higher than 38.3 °C on several occasions, and 3) the cause of which remains uncertain after one week of in-hospital diagnostic workup [1]. The first two criteria were meant to exclude viral diseases from the diagnosis of FUO, often acute and self-limited, and habitual hyperthermia. In response to the evolving trends in medical practice, however, the third criterion was redefined in 1991 as a fever remaining uncertain in spite of three outpatient visits or three days of in-hospital evaluation relevant for appropriate medical investigations [2]. Durack and Street later classified FUO into four diagnostic categories: classic, nosocomial, neutropenic, and human immunodeficiency virus (HIV)-associated FUO [2]. In older persons, these criteria are usually not satisfied because body temperature is frequently <38.8 °C and diagnostic procedures often last for more than one week.

As around 25% of FUO cases remain unsolved [3-5], the identification of FUO causes represents a great challenge for clinical practice, and this phenomenon is exacerbated by the difficulty of developing a universally accepted diagnostic algorithm for its differential diagnosis. Bleeker-Rovers et al. [6] reported a variable percentage from 7 to 53% of patients without a definitive diagnosis. Moreover, the term FUO should be used only when all the clinical examinations and appropriate investigations have failed to clarify the cause of fever, but sometimes clinicians get used to labelling it as FUO every time they don't find the underlying etiological component.

Epidemiological data on FUO are scarce in the literature. In 2003 a systematic review reported on case series and cohort studies conducted in tertiary care centres or community hospitals, aiming to develop evidence-based recommendations for the diagnostic workup of FUO [7]. This study included data from Europe (three studies), the Middle East (three studies) and the Far East (five studies) and reported a prevalence of FUO among hospitalized patients of 2.9%. The most common causes of FUO were: infections (28%), inflammatory diseases (21%), followed by undetermined diagnosis (19%) and malignancies (17%). Additionally, authors recommended to use the Duke criteria for endocarditis, computed tomographic scan of the abdomen, nuclear scanning with a technetium-based isotope, and liver biopsy (fair to good evidence) to address FUO diagnosis. Conversely, they didn't recommend routine bone marrow cultures.

Based on these observations, the aim of our study was to describe the epidemiology of classic FUO through the retrospective analysis of 902 861 admissions to a large University hospital in Italy; to analyse socio-demographic characteristics and health outcomes of patients with FUO; to investigate its temporal trend, and to evaluate differences between young and old patients affected by FUO.

METHODS

Our study was conducted at the university teaching hospital "A. Gemelli" in Rome. We retrieved the data records of all the admissions between the 1st January 1988 and 31st December 2007. Only admissions reported in the medical records as FUO were considered for the analysis, with two authors (NN, AS) independently reviewing the diagnosis of admission. Discrepancies between the two investigators were solved by oral discussion and consensus with a senior investigator (SB). In particular, "classic FUO" were included, in line with the definitions reported by the current literature [8]. Indeed, diagnoses of FUO in patients with a history of neutropenia and immunosuppressive diseases were excluded (e.g., HIV positive patient or transplantations). Nosocomial FUO were also excluded. For each case, we retrieved information on: age, number of transfers, departments of admission, length of stay, number of admissions (single or multiple admission for the same diagnosis), diagnosis on discharge and mortality. The admission rate of FUO was calculated as the number of admissions per year divided by the number of all the admissions to the hospital during the same time period. Data were stratified according to two age categories: 21-64 and ≥65 years old.

To identify the diagnosis on discharge of FUO cases, only data reported using the ICD9-CM code (International Classification of Diseases, Ninth Revision, Clinical Modification) were used [9]. The following codes were included: 038.9 (Unspecified septicaemia), 079.99 (Unspecified viral infection), 087.9 (Relapsing fever unspecified), 780.6 (Fever). We reported data as absolute and relative frequencies, and in proportion with the admissions of FUO. Discharge data were available only for the period 1995-2007.

Statistical analysis

Descriptive statistics were performed using frequencies, percentages, frequency tables for qualitative variables and mean ± standard error (SE) for quantitative variables. Proportional admission rates and time trends of FUO admissions were analysed by joinpoint regression, according to Kim's method [10, 11].

The following formula was used for the logarithmic transformation of rates:

$$\ln(y) = bx$$

where x represents the calendar years, b is the regression coefficient and y the proportional admission rate.

A joinpoint represents the time point when a significant trend change is detected. Time changes were expressed in terms of Expected Annual Percent Change (EAPC) with respective 95% confidence interval (95% CI); significance level of time trends was also reported. The null hypothesis was tested using a maximum of three changes in slope with an overall significance level of 0.05 divided by the number of joinpoints in the final model. Chi-square and Mann Whitney tests were used to analyze differences between qualitative and quantitative variables, respectively. A p-value of 0.05 or less was considered statistically significant. Statistical analyses were conducted using STATA 9.0 for Windows and the Joinpoint Regression Program (Version 3.3.1).

RESULTS

Since 1988 and up to 2007, 3 156 admissions, involving 2 570 patients, were registered because of FUO, based on 902 861 overall admissions. Among them, 1 618 were referred to males and 1 538 to females (M/F ratio=1.05), while 1 737 (55.07%) were between 21-64 years old and 829 (26.28%) ≥ 65 years old. The IR of FUO admissions in the overall time period was 3.50 per 1 000 (95% CI: 3.40-3.60), ranging from 0.03 (95%CI: 0-0.10) in 1988 to 7.98 (95% CI: 7.22-8.74) in 1999 (Table 1 and Figure 1).

The time-trend analysis showed two joinpoints, the first in 1995 and the second in 1998. In fact, from 1995 to 1998, there was a statistically significant increase in the proportional admission rate of FUO admissions, with an EAPC of 307.80 (95% CI: 89.66-776.84, p=0.002), while after 1998 a significant decrease (EAPC=-8.57, 95% CI: -10.37-6.73; p<0.001) was registered (Table 2).

Table 3 shows the number of transfers, departments of admission, length of hospitalization period and number of admissions for each patient diagnosed with FUO. Almost 90% had no transfer, though the elderly had the largest number compared with the younger groups (p=0.002). Overall, admissions with a FUO diagnosis were most commonly addressed to the Departments of Infectious Diseases (41.22%) and Internal Medicine (28.77%), followed by Rheumatology (3.17%) for patients aged 21-64 and Geriatrics (10.13%) for patients ≥65. The differences between age groups within Departments were statistically significant (p<0.001) (Table 3). Additionally, there was a statistically significant difference for the length of hospitalization between the age groups of 21-64 and ≥ 65 years old, with a mean (±SE) of 12.97 (±14.55) and 17.21 (±16.43) days, respectively (p<0.001). Some patients were admitted to "A. Gemelli" hospital more than once: in particular, 12.02% were admitted twice for FUO, 2.72% were admitted three times and 1.36% were admitted from between 4 and 12 times, though without statistically significant differences (p=0.34) (Table 3).

Based on 3 126 admissions between 1995 and 2007, 678 discharge diagnoses with FUO were reported between 1995 and 2007. Overall, only 21.69% admissions were discharged with the same diagnosis (23.10% and 12.99% respectively for age groups 21-64 and ≥65 years). The most common code used was 780.6 (Fever), accounting for around 90% of diagnoses, followed by 38.9 (Unspecified septicaemia), 79.99 (Unspecified viral infection) and 87.9 (Relapsing fever unspecified). Diagnosis of unspecified relapsing fever was established for patients ≥65 years (Table 4). Lastly, the mortality rate for the 2 570 patients

TABLE 1

PROPORTIONAL ADMISSION RATES (PAR) AND 95% CONFIDENCE INTERVALS (CI) OF FEVER OF UNKNOWN ORIGIN ADMISSIONS

YEAR	PAR PER 1 000 ADMISSIONS	95% CI
1988	0.03	(0.00-0.10)
1989	0.13	(0.00-0.26)
1990	0.03	(0.00-0.10)
1991	0.20	(0.04-0.35)
1992	0.10	(0.00-0.21)
1993	0.22	(0.06-0.38)
1994	0.25	(0.08-0.42)
1995*	0.18	(0.05-0.32)
1996	0.33	(0.16-0.50)
1997	0.60	(0.38-0.82)
1998*	7.57	(6.86-8.31)
1999	7.98	(7.22-8.74)
2000	7.42	(6.70-8.13)
2001	6.16	(5.51-6.81)
2002	5.68	(5.06-6.31)
2003	4.81	(4.24-5.39)
2004	4.07	(3.54-4.61)
2005	4.56	(4.00-5.12)
2006	4.42	(3.88-4.97)
2007	3.19	(2.73-3.65)
TOTAL	3.50	(3.40-3.60)

*=Joinpoints

was 2.53%, 1.75% for those aged 21-64 years old, and 5.86% among those ≥65 years old ($p<0.001$, data not shown).

DISCUSSION

This retrospective study was carried out to describe the epidemiology, characteristics and health outcomes of patients with FUO admitted to a large Italian university teaching hospital between 1988 and 2007. The overall proportional admission rate of FUO diagnoses was 3.50 per 1 000 admissions: 3 156 cases were diagnosed, of these 55.07% were aged 21-64 years, while 26.28% were ≥65 years. The rate for the elderly group could be underestimated because, among these patients, a body temperature higher than 38.3 °C is less common, being this difference due to the age-related modifications in thermoregulation [12].

Our data showed two joinpoints: from 1995 to 1998 an increase of the proportional admission rates of FUO was observed, followed by a decrease after 1999. The first trend could be attributed to the introduction of the Diagnosis Related Groups classification system in the Italian healthcare system in 1994 [13], that improved the use of specific diagnostic codes related to fever.

The second trend might be due to several improvements in new diagnostic techniques such as rapid antigen assays and polymerase chain reaction (PCR) that made possible more accurate and rapid diagnoses of infections.

Regarding the numbers of transfers and the length of hospitalization, we observed significant differences between the age groups of 21-64 and ≥65 years old. Older patients were more commonly transferred and had prolonged hospital stays (>17 days), with a higher resulting mortality rate compared with younger patients. It is known that hospitalized aged patients are vulnerable to many conditions

FIGURE 1

PROPORTIONAL ADMISSION RATES (PAR) OF FEVER OF UNKNOWN ORIGIN ADMISSIONS (1988-2007)

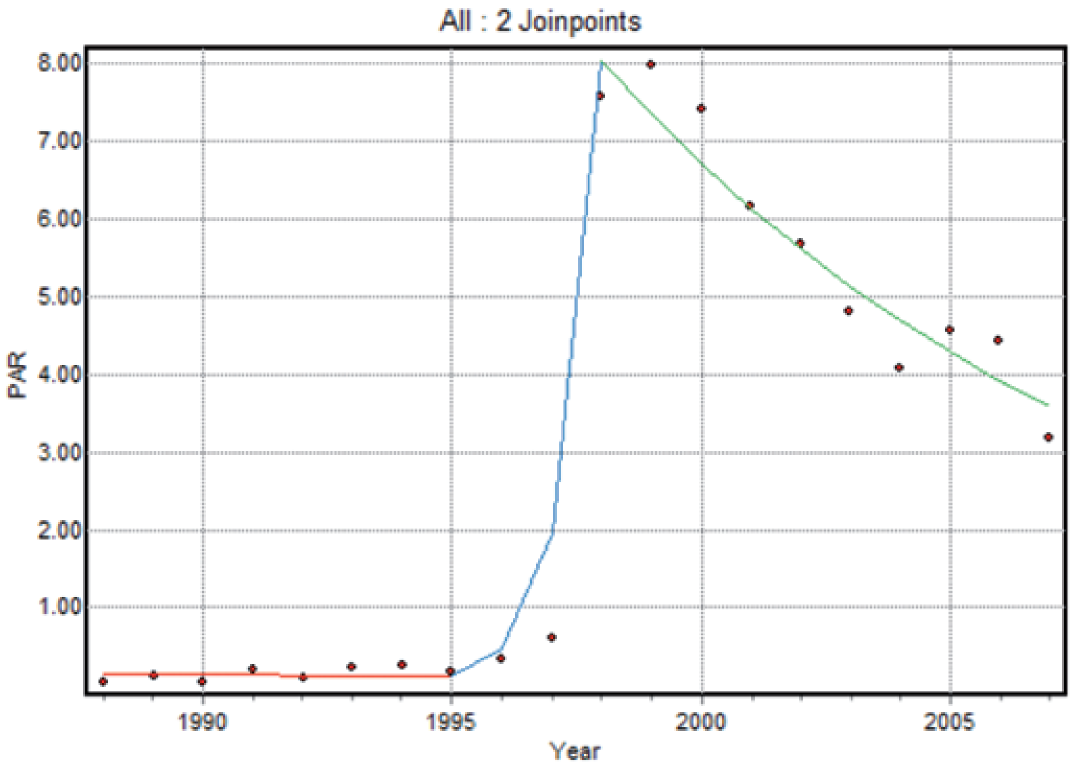

TABLE 2

EXPECTED ANNUAL PERCENT CHANGE (EAPC) AND 95% CONFIDENCE INTERVAL (CI) OF FUO ADMISSIONS

YEARS RANGE	EAPC	95%CI	p-VALUE
1988-1995	-2.94	(-20.30; 18.20)	0.75
1995-1998	307.80	(89.66; 776.84)	<0.002
1998-2007	-8.57	(-10.37; -6.73)	<0.001

potentially bringing to functional decline [14]. Inouye et al. [15] reported that 34% to 50% of hospitalized older adults have poor health outcomes, which determine a long hospital stay and increase hospital costs and mortality rates. Moreover, a trial conducted by Landefeld et al., showed that it is important to adopt special changes in the provision of acute hospital care, such as a patient-centered care emphasizing independence, including specific protocols for prevention of disability and for rehabilitation, to improve functional outcomes of acute older patients and to reduce the frequency of discharge to institutions for long-term care [16].

In our study the majority of admissions with FUO were addressed to the Department of Infectious Diseases (41.22%), and the Departments of Internal Medicine (28.77%), which is in agreement with that reported by Williams et al. [17-19]. As expected, we observed a significant difference between two age groups concerning the admission departments: Internal Medicine and Geriatrics hosted 29.88% of 21-64 years versus 42.22% of ≥65, and 1.87% versus 10.13%, respectively ($p<0.001$). Our study reports that around 22% of admissions remained without a definitive diagnosis, which is in accordance with the literature [17-20]. This percentage was lower in patients ≥65 years (around 13%) compared with

TABLE 3

NUMBER OF TRANSFERS, DEPARTMENTS, LENGTH OF STAY AND NUMBER OF ADMISSIONS FOR FUO ACCORDING TO AGE GROUPS

	FUO ADMISSIONS		
NUMBER OF TRANSFERS	OVERALL (n=3 156)	21-64 YEARS (n=1 737)	≥65 YEARS (n=829)
	n(%)	n(%)	n(%)
0	2 763 (87.55)	1 532 (88.20)	687 (82.87)
1	291 (9.22)	149 (8.58)	103 (12.42)
2	59 (1.87)	36 (2.07)	20 (2.41)
≥3	43 (1.36)	20 (1.16)	19 (2.29)
*p-value**		0.002	
DEPARTMENTS			
Infectious Diseases	1 301 (41.22)	949 (54.63)	253 (30.52)
Internal Medicine	908 (28.77)	519 (29.88)	350 (42.22)
Paediatrics	413 (13.08)	-	-
Geriatrics	115 (3.64)	31 (1.78)	84 (10.13)
Rheumatology	98 (3.11)	55 (3.17)	34 (4.10)
Surgery	77 (2.44)	55 (3.17)	18 (2.17)
Others	244 (7.73)	128 (7.37)	90 (10.86)
*p-value**		<0.001	
LENGHT OF STAY (DAYS)	MEAN±SE	MEAN±SE	MEAN±SE
	13±14.55	12.97±14.55	17.21±16.43
*p-value***		<0.001	
	FUO PATIENTS		
NUMBER OF ADMISSIONS	(n=2 570)	21-64 YEARS (n=1 432)	≥65 YEARS (n=665)
	n(%)	n(%)	n(%)
1	2 156 (83.89)	1 224 (85.47)	548 (82.41)
2	309 (12.02)	152 (10.61)	87 (13.08)
3	70 (2.72)	37 (2.58)	20 (3.01)
4-12	35 (1.37)	19 (1.33)	10 (1.51)
*p-value**		0.34	

* Chi-Square test
** Mann Whitney test

patients aged 21-64 years (23.10%) (p<0.001).

It would be necessary to define guidelines or evidence-based recommendations to determine the specific cause of FUO. Nowadays, there is no diagnostic gold standard to determine FUO causes and clinicians make their diagnoses in very different ways: some of them include natural history, biopsy, surgery, postmortem examinations as well as several imaging and laboratory techniques [7]. Interestingly, Gaeta et al. [20] proposed a standardized flow chart to solve the FUO issue, to be applied only in absence of potential diagnostic clues or when these are contradictory. In our study pediatric patients were not considered, as there is no consensus about the optimal management of infants and young children with FUO. Two decision analyses [21, 22] indicate that an optimal strategy would be to carry out blood culture and start empiric antibiotic treatment (including empirical therapy with anti-tuberculosis drugs), but many clinicians disagree with this strategy [23].

Because of the large sample size of the study, its characteristics (broad range of patient's age, long period of recruitment) and the study setting (large university teaching hospital), this makes it possible to apply our

TABLE 4

DIAGNOSIS OF DISCHARGE OF FUO ADMISSIONS, ACCORDING TO AGE GROUPS (YEARS 1995-2007)	ALL AGES (n=678)*		21-64 YEARS (n=398)		≥65 YEARS (n=107)	
	n(%)	% RESPECT TO THE ADMISSION WITH FUO	n(%)	% RESPECT TO THE ADMISSION WITH FUO	n(%)	% RESPECT TO THE ADMISSION WITH FUO
UNSPECIFIED SEPTICAEMIA (38.9)	40 (5.90)	1.28%	19 (4.77)	1.10%	18 (16.82)	2.18%
UNSPECIFIED VIRAL INFECTION (79.99)	25 (3.69)	0.80%	16 (4.02)	0.93%	2 (1.87)	0.24%
RELAPSING FEVER UNSPECIFIED (87.9)	5 (0.74)	0.16%	2 (0.50)	0.12%	-	-
FEVER (780.6)	608 (89.68)	19.45%	361 (90.70)	20.95%	87 (81.31)	10.56%
TOTAL	678 (100.00)	21.69%	398 (100.00)	23.10%	107 (100.00)	12.99%

Chi square test between age groups, $p<0.001$*Discharge data were available only for the period 1995-2007

findings to other settings and populations. Some limitations of this study, however, should be acknowledged. Some limits are inherent to the retrospective nature of the study design, such as inappropriate data collection and recording methods. The definition of FUO is based only on the duration of diagnosis time: is not based on any medical investigations performed before defining a patient as affected by FUO. Moreover the diagnostic algorithm is not based on any specific flow-chart, but the role of potential diagnostic clues (PDCs) are increasingly emphasized if designing a specific diagnostic strategy [19]. Recently, the role of (18)F-FDG PET/CT in the identification of an underlying cause of the fever has been shown to contribute to the diagnosis or exclusion of a focal pathologic aetiology of the febrile state in a high percentage of patients, with a high negative predictive value. Nowadays it is considered as third level diagnosis, but, if confirmed by other studies, it may be used in the future as an initial non-invasive diagnostic modality for the assessment of this group of patients [24, 25]. Before undertaking a diagnostic evaluation of FUO, it is important to consider the patient's overall health. It's more important to maintain a patient's quality of life than it is to initiate the process of identifying the underlying cause of a persistent fever. A greater effort is required to improve the diagnostic accuracy of FUO among older patients hospitalized with fever and identify patients at high risk for adverse health outcomes. The work-up should not be worse than the disease.

In conclusion, FUO still represents a significant cause of admissions to hospital, because of the proportion its size represents as well as its related morbidity and mortality; it thus represents a critical challenge for diagnostic medicine, so further research and many efforts are needed to achieve the goal of developing a diagnostic methodology for FUO, in order to reduce costs of preventable hospitalizations. Nevertheless, as most cases are due to unusual presentations of common diseases, rather than rare diseases, a careful clinical history, the systematic search of potential diagnostic clues (PDCs), together with targeted investigations, have still a key role to play in the achievement of a correct diagnosis. The development of specific expertise or centres for FUO by an approach aimed at the problem can bring about improvement in terms of percentage of diagnosis identification, and mortality reduction, particularly for older patients, as confirmed by the experiences of the Centres of London and Bethesda [17].

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