Medicine®

Long-term prognosis, treatment, and outcome of patients with fever of unknown origin in whom no diagnosis was made despite extensive investigation

A questionnaire based study

Catharina M. Mulders-Manders, MD[a,b,*], Celeste Engwerda, MD[a], Anna Simon, MD, PhD[a,b], Jos W.M. van der Meer, MD, PhD[a,b], Chantal P. Bleeker-Rovers, MD, PhD[a,b]

Abstract

In 30–50% of patients with fever of unknown origin (IUO) no explanation for the fever can be found. Prognosis and effects of empirical treatment of these patients are largely unknown.

With this retrospective, questionnaire based corort study in all unexplained FUO patients in an expert center between 2003 and 2014 we studied mortality and outcome.

In 131 of 274 FUO patients, FUO remained unexplained. Ninety-nine of them responded to the long-term follow up questionnaire. Adter a median duration of follow-up of 60 months, spontaneous remission of fever occured in 47.3%. Empirical treatment was effective in 66.7% of patients. Mortality was 6.9%. The cause of death was considered not to be related to the febrile disease in five out of six patients. Ten out of 99 responders reported to have received a final explanation for FUO after evaluation in the expertise center, but this diagnosis could not be confirmed in six cases and was considered to be an unlikely explanation for FUO in four out of six cases.

We conclude that mortality in unexplained FUO is low en mostly unrelated to the febrile disease. Spontaneous resolution of fever is common. Empirical treatment prescribed by an expert physician is often effective, but should be avoided untill all diagnostic possibilities have been exhaused.

Abbreviations: FUO = fever of unknown origin, IUO = inflammation of unknown origin.

Keywords: fever of unknown origin, mortality, prognosis, survival, therapy, treatment

1. Introduction

Fever of unknown origin (FUO) and inflammation of unknown origin (IUO) are complex diagnostic problems encountered by many different medical specialists. FUO/IUO is defined as at least 3 weeks duration of fever or elevated inflammatory markers in an immunocompetent patient, for which no cause is found despite an extensive workup.[1–4] (Table 1).

In recent Dutch and other western-European cohorts,[1,5–9] 30% to 50% of patients remain undiagnosed despite extensive

[a] Department of Internal Medicine, [b] Expertise Center for Immunodeficiency and Autoinflammation, Radboud University Medical Center, Nijmegen, the Netherlands.

* Correspondence: Catharina M. Mulders-Manders, Department of Internal Medicine, Radboud University Medical Center, 463, PO box 9101, 6500 HB Nijmegen, the Netherlands (e-mail: Karin.Mulders-Manders@radboudumc.nl).

evaluation. The prognosis of these patients is not well known. The only western-European study specifically designed to determine the prognosis of FUO patients reported a mortality of 2.4% in 168 undiagnosed patients. In that study, all deaths in patients with unexplained FUO occurred during the index admission.[10]

Although spontaneous resolution of FUO was reported in 43% to 75% of undiagnosed cases[1,3,6,11], many patients with undiagnosed FUO are empirically treated with antibiotics, corticosteroids, or other anti-inflammatory drugs. The effects of these treatments are largely unknown.

We performed a questionnaire-based long-term follow-up study on treatment and prognosis in patients with FUO that remained undiagnosed during the 2 most recent Dutch FUO studies.[1,9]

2. Materials and methods

2.1. Patient selection

All patients that remained undiagnosed in the 2 most recent Dutch FUO studies were eligible for inclusion. Both studies were performed in the Radboud university medical center, a 630-bed tertiary referral center and expertise center for FUO. These 2 studies included 245 patients with FUO and 64 patients with IUO. Inclusion criteria are described in detail elsewhere.[1,9]

2.2. Medical ethics approval

This study was assessed by the medical ethics committee Arnhem-Nijmegen (registration number 2014/309) and according to

Mulders-Manders et al. Medicine (2018) 97:25

Medicine

Dutch law it was exempt from approval and the collection of written informed consent because of its non-invasive design and anonymous storage of patient data.

2.3. Data collection

2.3.1. Medical records. Demographic data and data on FUO, including age of onset, date of first presentation, fever pattern, treatment, outcome, and survival were collected from the medical records.

2.3.2. Surveys. Eligible patients were contacted by phone. A standardized interview (English translation in Supplement 1, http://links.lww.com/MD/C308) was performed. If calls remained unanswered, a standardized questionnaire including the same questions as the telephonic interview was sent out either by regular mail or email. A prepaid pre-addressed return envelope was included in all surveys sent out by regular mail. E-mails contained a hyperlink to a secured online survey. Patients that did not complete the survey within 2 weeks were sent a reminder. Online survey responses were only included in the analyses if they were fully completed.

If patients reported to have visited another hospital because of FUO or IUO after the end of the FUO study, they were asked permission to approach the health-care provider to collect relevant medical data. If patients gave consent, they were sent a paper informed consent form and prepaid pre-addressed return envelope. These forms were used to collect relevant medical data from other hospitals. The proof of the diagnosis and the likelihood of being related to FUO were discussed between all investigators for all final diagnoses until consensus was reached. Diagnoses were categorized as confirmed when considered sufficiently validated based on the collected data. If insufficiently proven, diagnoses were categorized as unconfirmed.

Patients had not been instructed to regularly measure their body temperature, but did so on their own initiative. Continuous fever or inflammation was considered cured if patients had been fever or symptom free for at least 1 week at the time of the questionnaire. Recurrent fever or inflammation was considered cured based on the individual fever or inflammation pattern. If any information on remission of fever or inflammation was unclear, it was discussed between the investigators until consensus was reached.

For patients responding to the questionnaire, duration of follow up was defined as the time between the first presentation to the Radboudumc and the date on which the questionnaire was completed. For non-responders, duration of follow up was defined as the interval between the first presentation and the last contact with the Radboudumc during the FUO study.

2.4. Statistical analysis

Categorical data are represented as number (percentage) and compared by Fisher exact test. Continuous data are represented as median (range) and compared using two-tailed Mann–Whitney U test. A P-value of $<.05$ was considered statistically significant. Statistical analyses were performed using SPSS for Windows, version 22.0 (IBM, Armonk, New York).

3. Results

3.1. Patient characteristics

The 2 most recent Dutch cohort studies on FUO/IUO included a total of 274 patients, in 131 (47.8%) of which the cause for the fever or inflammation remained unknown. Sixty-three patients with unexplained FUO (48.1%) were men. Total median duration of follow up was 60 months (range, 0–177 months). (Table 2).

3.2. Prognosis during FUO study

3.2.1. Treatment during FUO study. Median duration of follow-up during both FUO studies was 18 months (range, 0–58 months). Fifty-three of the 131 patients with unexplained FUO (40.5%) were treated during the FUO studies. Steroids and drugs in the category other drugs were the most commonly used (N=26, 19.8%) (Table 3).

Of all 53 patients that received at least 1 treatment for unexplained FUO during the FUO study, 11 (20.6%) did not respond to the questionnaire. Remission of fever upon treatment was noted in the medical chart in 4 of them (36.6%).

Of the 71 patients that remained untreated during the FUO study, 11 (15.4%) did not respond to the questionnaire. In 7 of these patients (63.6%) spontaneous remission of fever was noted in the medical charts. Median duration of fever in these patients was 3.5 months (range 0–38 months).

3.2.2. Survival. Three patients (2.3%) died during the FUO studies. The cause of death remained unknown in 1. The 2 other patients died of heart failure, which was regarded unrelated to the

---

Table 1

Definition of fever of unknown origin (FUO) and inflammation of unknown origin (IUO)[1–4].

1. On several separate occasions:
   - Fever ≥38.3°C (≥101°F) (for FUO) OR
   - Elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or serum amyloid A (SAA) with body temperature <38.3°C (<101°F) (for IUO)
2. Duration of illness at least 3 weeks
3. No diagnosis despite extensive evaluation including (but not limited to):
   Extensive medical history and physical examination
   Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) or serum amyloid A (SAA), hemoglobin, platelet count, leukocyte count including differentiation, sodium, potassium, calcium, creatinin, total serum protein en protein electrophoresis, alkaline phosphatase (AF), aspartate aminotransferase (ASAT), alanine aminotranspherase (ALAT), lactate dehydrogenase (LDH), creatinin kinase (CK), antinuclear antibodies (ANA), rheumatoid factor (RF), microscopic urinalysis, ferritin
   Blood cultures (minimal 3), urine culture, tuberculin skin test or interferon gamma release assay
   Chest x-ray, abdominal ultrasound, or chest and abdominal CT scan
4. No known immunocompromised state, excluding the following:
   Neutropenia (leukocyte count $<1.0 \times 10^9$/L or granulocyte count $<0.5 \times 10^9$/L) during at least 1 week within the 3 months before the start of the fever
   Known human immunodeficiency virus (HIV) infection
   Known hypogammaglobulinemia (IgG <50% of normal value)
   Use of 10 mg prednisone or equivalent dose of corticosteroids during at least 2 weeks in the 3 months before the start of the fever

Mulders-Manders et al. Medicine (2018) 97:25

www.md-journal.com

Patient characteristics of 131 patients that remained undiagnosed during previous Dutch fever of unknown origin studies.

		All patients N=131	Responders N=99	Non-responders N=32	P-value[*]
Gender	Male	63 (48.1%)	46 (46.5%)	17 (53.1%)	.55
Fever pattern	Continuous	32 (24.4%)	23 (23.2%)	9 (28.1%)	.64
	Episodical	99 (75.6%)	76 (76.8%)	23 (71.9%)	
Median age at start fever (range)		44 (0–87)	44 (0–81)	43 (0–87)	.50
Median age at first study contact (range)		45 (18–87)	45 (18–81)	47 (19–87)	.80
Duration of FUO/IUO at first presentation (months, [range])		12 (0–579)	17 (0–579)	6.5 (0–337)	.016
Median duration of follow up in FUO study (months, [range])		20 (0–169)	20 (0–169)	18 (0–58)	.42
Median duration of total follow up (months, [range])		60 (0–177[†])	75 (28–177)	18 (0–58)	<.001
Study type	Telephone	84 (64.1%)	84 (84.8%)	N/A	N/A
	Online	10 (7.6%)	10 (10.1%)	N/A	N/A
	Post	5 (3.8%)	5 (5.1%)	N/A	N/A
	No current contact information available	2 (1.5%)	N/A	2 (6.3%)	N/A
Participant	Patient	93 (71.0%)	93 (93.9%)	N/A	N/A
	Family member	6 (4.6%)	6 (6.1%)	N/A	N/A

FUO = fever of unknown origin, IUO = inflammation of unknown origin, N/A = not applicable.

[*] Responders versus non responders.

[†] One patient exceeded the maximum duration of follow up of 157 months (from 2003 to 2016). This patient presented with FUO in 2001 and was included in the FUO study in 2003 when PET/CT was made because of still unexplained FUO.

underlying cause of the fever, after 38 and 42 months from presentation, respectively. (Table 4).

3.3. Prognosis during long-term follow-up

Ninety-nine of the 131 patients with unexplained FUO (75.6%) responded to the questionnaire for long-term follow-up. Median

Treatment and efficacy of treatment in patients with unexplained FUO[*].

Treatment	Number of patients during FUO study (%) N=131	Number of patients after FUO study (%) N=99	Effectiveness (%)[†]
Antibiotics	14 (10.7%)	3 (3.0%)[‡]	12 (70.6%)
NSAIDs/acetaminophen	17 (13.0%)	3 (3.0%)[‡]	13 (65.0%)
Corticosteroids	26 (19.8%)		22 (84.6%)
Immunosuppressive drugs	6 (4.6%)		4 (66.7%)
Etanercept	1 (0.8%)		
Infliximab	1 (0.8%)		
Methotrexate	3 (2.3%)		
Tocilizumab	1 (0.8%)		
Anakinra	20 (15.3%)	1 (1.0%)	14 (66.7%)
Chemotherapy	2 (1.5%)		0
Other drugs	26 (19.8%)	2 (2.0%)	15 (53.6%)
Colchicine	15 (11.5%)		
Other treatment	3 (2.3%)		4 (100%)
Psychotherapy	2 (1.5%)		
Oral anticonceptives	1 (0.8%)	1 (1.1%)[‡]	
Acupuncture			
Median			66.7%

FUO = fever of unknown origin, NSAIDs = non-steroidal anti-inflammatory drugs.

[*] Patients could have used several kinds of drug during follow up.

[†] Effectiveness was defined as at least temporarily effect on fever/inflammation and complaints.

[‡] These patients reported this treatment for FUO in the questionnaire. As starting dates were unknown and these treatments were not registered during the FUO study, it was unclear whether this treatment was initiated before or after the FUO study.

duration of follow-up in these patients was 75 months (range 28–177 months). (Table 2)

3.3.1. Treatment during long-term follow-up. Fifty-three of the 64 patients that received some form of treatment for unexplained FUO during the FUO study (82.8%) responded to the questionnaire. Twenty-eight of them (52.8%) reported that their fever had resolved. Median duration from the start of the fever to remission was 21 months (range 0–86 months).

Forty-six patients who remained untreated during the FUO study responded to the questionnaire and 20 of them (43.5%) reported spontaneous remission of fever. In untreated patients, median duration of fever was 2.0 months (range 0–45 months). This was not significantly different from treated patients (P=.19).

Ten of the 99 responders (10.1%) reported to have received some form of treatment for unexplained FUO that was not reported during the FUO studies (Table 3). In only 3 of them treatment was definitely started after the FUO study. One of these 3 reported to have been prescribed anakinra, the second used omalizumab and the third one reported to have been treated with nadroparine and acenocoumarol, all 3 in absence of an explanation.

Of all empirical treatments, 66.7% had been effective (Table 3).

3.3.2. Survival during long-term follow-up. Six patients (6.1%) died during long-term follow-up (Table 4). Median duration from first presentation to death was 13 months (range 3–24 months) and median age at death was 73 years (range 64–79 years). The cause of death was known in 4 patients and was considered unrelated to FUO in 3 of them. In 1 patient, who died from breast cancer, it was unclear whether the tumor could have been responsible for the febrile illness (Table 4).

3.3.3. Further investigation during long-term follow-up. Twenty-six of 99 responders (26.3%) reported to have visited another health-care provider because of FUO after the FUO study. These patients had visited a median of one health-care provider (range 1–3 providers).

Table 4

Characteristics of undiagnosed patients with fever of unknown origin that died.

	Gender, age at presentation	Duration from presentation to death (mo)	Cause of death (source)	Fever at time of death	Death related to FUO
1	M, 81*	38	Congestive heart failure due to previous and recent myocardial infarction with pre-existing valvular heart disease, pulmonary hypertension and pulmonary embolism. No signs of endocarditis. (Autopsy report)	No, remission on therapy	No
2	M, 78*	42	Congestive heart failure upon rehydration therapy. Dehydration upon refusal of oral intake due to oral pemphigus vulgaris (medical record)	No, spontaneous remission	No
3	M, 81*,†	?	Unknown (nonresponder)	Unknown	Unknown
4	M, 69	6	Congestive heart failure associated with pneumonia and Lewy body dementia (medical record)	Yes, no therapy	No
5	M, 63	13	Unknown heart disease (family member)	Yes, despite therapy	No
6	M, 77	3	Cardiac arrest (family member)	Yes, despite therapy	No
7	F, 77†	24	Breast cancer (family member)	Unknown	Unknown
8	M, 72†	16	Unknown (nonresponder)	Unknown	Unknown
9	M, 87†	?	Unknown (nonresponder)	Unknown	Unknown

F = Female, M = Male, FUO = fever of unknown origin.

* This patient died during the FUO study.

† This patient had been included in the FUO study by Bleeker-Rovers et al[1] from a community hospital and further data were unavailable.

Ten patients (10.1%) reported that a final diagnosis had been made after the FUO study (Table 5). Median duration from the first visit to the Radboudumc to the final diagnosis was 3 years (range 0.6–11 years). In 6 of the 10 patients that reported a diagnosis after the FUO study (60.0%), the diagnosis could not be confirmed after further investigation. Of all 6 unconfirmed diagnoses, 4 (66.7%) were considered unlikely to be related to FUO, 1 (16.7%) was considered possibly related to FUO, and 1 (16.7%) was considered a likely explanation for the FUO (Table 5).

4. Discussion

Of the 131 patients with FUO that remained unexplained in the 2 most recent Dutch FUO studies,[1,9] 9 died during a median follow up of 5 years. In untreated patients, spontaneous remission of fever was present in 47.3%.

Little is known on the prognosis of patients with unexplained FUO/IUO. Only a single study specifically designed to address prognosis in FUO has been performed until now.[10] In this study 4 of 168 patients with unexplained FUO died during a follow up of at least 6 months, and in only 2 cases no diagnosis could be made upon autopsy. A previous and smaller Dutch FUO study has shown mortality rates of 4.0%.[11] Other western-European studies showed mortality rates between 2.0% and 19.0% in unexplained FUO.[3,5–8] The differences between these studies may arise from differences in patient selection, study design, and differences in health care systems. With a median follow up of 60 months, our study has the longest duration of follow up of all recent FUO studies.

In the 6 patients that died with a known cause of death, death was considered unrelated to the febrile disease in 5. All of these patients died from a frequently seen cardiac disease. In the sixth patient it remains unknown whether the breast cancer she died from could have been present at the time of FUO.

Spontaneous remission of FUO/IUO occurred in 47.3% of untreated patients. In other western-European studies this percentages varies between 15% and 88%,[3,5–7,11–13] and in

non-western European studies between 15% and 100%.[14–19] The wide range of duration of fever shows that it may take a long time until fever resolves.

Empirical treatment was effective in 66.7% of patients, with a median duration of fever of 21 months. Based on the wide range of duration of fever, it could be debated whether the empirical treatment was truly effective, as it cannot be proven that the fever would have resolved spontaneously.

In 2 of the 3 patients reporting to have been treated for FUO after the FUO study, treatment with either anakinra or omalizumab was considered related to FUO, but was questionable in the third one, reporting having used acenocoumarol and nadroparine in absence of a diagnosis. Of these 3 patients, only in the patient that was started on omalimumab the reason for the start of this therapy was known: chronic urticaria in absence of a definite diagnosis.

It could be debated whether the empirical therapy initiated for unexplained FUO in the 2 recent Dutch FUO studies could have influenced the diagnostic yield in these studies. Of the 99 responders in this study, 26.3% reported to have visited another health care provider because of FUO after no explanation for FUO had been found in our FUO expertise center. This illustrates that the vast majority of patients with FUO/IUO is sufficiently reassured when no diagnosis can be found in an FUO expertise center. Ten out of the 99 patients in our study reported to have received a final diagnosis for their FUO/IUO after the FUO study, but this diagnosis was considered not to be related to the FUO in half of them. Diagnoses with possible relation to FUO were recurrent aspiration, drug fever, *Streptococcus viridians* bacteraemia, thyroiditis, and familial Mediterranean fever. The diagnoses recurrent aspiration and *S viridians* bacteraemia may have been masked by the use of antibiotics, but 1 of these 2 patients had not been treated with antibiotics during the FUO study. Of all 5 patients with an unlikely diagnosis, 1 patient had been diagnosed with Hodgkin lymphoma, and this patient had been treated with corticosteroids during the FUO study. However, the PET/CT that showed no signs of lymphoma during the FUO study, and the interval between presentation and

Table 5

Reported diagnoses made after fever of unknown origin study.

	Gender, age* (y)	Fever pattern	Diagnosis†	Diagnostic category	Treatment	Heath care provider	Duration until diagnosis (mo)‡	Opinion on likelihood of relation to FUO§
1	F, 50	Continuous	Aspiration pneumonia due to hiatus hernia (confirmed)	Infection	Fundoplication	Community hospital	135	Likely explanation for FUO. After analysis by a gastroenterologist, fundoplication because of hernia diaphragmatica was performed, after which the patient never had fever again. Confirmed by data received from the respective consultant.
2	F, 68	Recurrent	Drug fever on rosuvastatin (confirmed)	Miscellaneous	Stop rosuvastatin	General practitioner	12	Likely explanation for FUO. The patient reported she became fever free after stopping rosuvastatin, which she used during FUO evaluation. Confirmed by her primary physician.
3	F, 71	Recurrent	Recurrent *S viridans* bacteriemia (confirmed)	Infection	Antibiotics, dental extraction	FUO expertise center	12	Likely explanation for the fever. Approximately 1 year after the FUO study, the patient had a fever episode with *S viridans* bacteremia. PET/CT showed no contributory findings, but X-OPT showed lucent areas in the maxilla. After extraction of all teeth, the patient became afebrile
4	F, 50	Recurrent	Ankylosing spondylitis (confirmed)	NIID	None	Community hospital	136	Relationship unlikely due to long time-interval. Patient suffered from episodical back pain during FUO evaluation. PET/CT was normal. Diagnosis was confirmed by treating physician.
5	F, 47	Continuous	Thyroiditis and endometriosis (unconfirmed)	Other	Levothyroxin and uterus extirpation	Community hospital	6	Likely explanation for the fever. During FUO evaluation PET/CT showed increased FDG-uptake in the thyroid. Biopsy showed lymphocytic thyroiditis. Subclinical hypothyreoidism was present. During the study, she did not report to have become fever free upon the start of levothyroxin, but now she is, and after stopping levothyroxin she reported to become febrile again. Approximately at the same time as the start of levothyroxin, uterus extirpation was performed.
6	M, 28	Recurrent	FMF (unconfirmed)	NIID	Colchicine, anakinra	Hospital in other country	29	Possible explanation for the fever This Turkish patient went to a consultant in Turkey, where amyloidosis was found in a skin biopsy. Mutation analysis for FMF was normal (2011) and the clinical picture is not fully consistent with FMF. He could also suffer from Behcet disease, as HLA-B51 is positive. Colchicine is not fully effective, but anakinra is.
7	M, 33	Recurrent	Pulmonal fungal infection (unconfirmed)	Infection	Antibiotics	Community hospital	53	Relation unlikely because of long time interval. Patient reported that a pulmonal fungal infection was diagnosed in a Dutch community hospital. He did not consent to the transferral of further data from this hospital to the study center. During FUO evaluation he had a cough. PET/CT showed 2 pulmonary non-FDG-positive nodules. No sputum cultures or other microbiological evaluations were performed.
8	M, 41	Recurrent	Hodgkin lymphoma (unconfirmed)	Malignancy	Chemotherapy	Community hospital	42	Relation unlikely because of long time interval. During FUO evaluation 2 chest CTs, 2 abdominal CTs, and a cerebral MRI showed no contributory findings. PET/CT before referral had shown slightly increased uptake in multiple lymph nodes and spleen, but 2 months later PET/CT in the Radboudumc was normal. Bone

(continued)

Mulders-Manders et al. Medicine (2018) 97:25

Medicine

Table 5
(continued).

Gender, age* (y)	Fever pattern	Diagnosis†	Diagnostic category	Treatment	Health care provider	Duration until diagnosis (mo)‡	Opinion on likelihood of relation to FUO§
							marrow aspirate before referral had been normal. No lymph node biopsy had been done.
9	F, 68	Recurrent	Q-fever (unconfirmed)	Infection	None	Community hospital	24	Relationship unlikely. Q-fever serology IgM and IgG had been normal during FUO evaluation. We did not receive any data from the consultant who diagnosed this patient.
10	F, 63	Recurrent	Drug fever on acetaminophen or NSAIDs (unconfirmed)	Miscellaneous	Stop acetaminophen and NSAIDs	Self diagnosis	49	Relationship unlikely. The patient reported that she became febrile minutes after ingestion of NSAIDs/acetaminophen and became fever free after cessation of these drugs. Pathophysiologically the relation is very unlikely, but fever is a reported rare side effect of acetaminophen (0.1–1% of cases)

F = Female, FMF = Familial Mediterranean fever, FUO = fever of unknown origin, M = male, NIID = non-infectious inflammatory disease, NSAIDs = non-steroidal anti-inflammatory drugs.
* Age at first presentation at Radboudumc.
† Diagnosis was confirmed if correspondence from the health care provider who made the diagnosis showed definite proof. Diagnosis was considered unconfirmed if correspondence did not show definite proof or no correspondence was received from the diagnosing health care provider.
‡ From the first presentation at Radboudumc to diagnosis.
§ Subjective opinion of the study team on the likeliness that the diagnosis was related to the episode(s) of FUO.

diagnosis of 3.5 years make a relation with FUO unlikely and it is, therefore, implausible that this diagnosis was missed during the FUO study.

Although the data from this study illustrate effectiveness of for instance corticosteroids in patients with FUO/IUO, empirical treatment should be used with extreme caution in FUO/IUO patients. Making a final diagnosis is of foremost importance and should have priority above empirical treatment, as making a final diagnosis may lead to different life-saving treatment choices. A classical example of this is lymphoma, in which corticosteroids may lead to remission of fever and may also reduce tumor mass, but without full cure. Steroids may mask important diagnostic clues, decreasing the chance of making a final diagnosis and initiation of life-saving therapy. Besides that, corticosteroids and other immunosuppressive drugs frequently have serious infectious and metabolic side effects. Because of this, empirical therapy should be postponed until all diagnostic possibilities have become exhausted and clinical deterioration is present. In the current study, all therapeutic choices were based on expert opinion, usually after discussion among the FUO experts in our center. What type of drug to use for empirical treatment largely depends on the clinical picture, the experience of the treating physician, and the presence or absence of a strongly suspected but impossible to prove diagnosis. In the current study 20% of patients were treated with corticosteroids. This is similar to other western-European FUO studies, were 8.1% to 40.9% of undiagnosed patients received these drugs.[6,8,20] Fifteen percent of patients in the current study were treated with the interleukin-1 receptor antagonist anakinra. This drug is effective in auto-inflammatory diseases. An increasing number of these are described in literature, but a significant proportion of patients with clear symptoms of autoinflammation cannot be diagnosed with one of the known autoinflammatory diseases, as these diseases are extremely rare and there are no investigations, besides genetic mutation analysis in some autoinflammatory diseases, that can definitely prove the presence of autoinflammation. After exclusion of other causes, anakinra could be tried in patients with symptoms of autoinflammation, such as fever, skin rash, and/or serositis.[21] In most autoinflammatory diseases, anakinra has a rapid and substantial effect on fever and other symptoms. A rapid positive reaction to anakinra almost certainly proves the presence of autoinflammation, which is caused by overproduction of interleukin-1. The effectiveness of 66.7% found in this study illustrates that experts on this type of diseases are able to distinguish autoinflammation from other causes of FUO.

The main limitation of this study is its retrospective questionnaire-based design, which may induce selection and recall bias. To overcome this limitation, we compared the results from the questionnaires to results from medical charts. The study's long duration of follow-up did not induce a significant loss to follow-up, as 75% of all undiagnosed FUO patients seen between 2003 and 2014 responded to the questionnaire. Furthermore, in patients that did not respond to the long-term follow-up questionnaire, data from available medical charts were used to complete missing data.

In conclusion, during a median follow up of 60 months, mortality in undiagnosed FUO/IUO patients was low and mostly unrelated to the febrile disease. Spontaneous resolution of fever occurs in approximately half of undiagnosed patients, but may take a long time to become apparent. Empirical treatment can be effective, but should be postponed in favor of making a final diagnosis, which may influence prognosis.

Author contributions

CM designed the study, collected data, analyzed the data, and drafted first and following version of manuscript. CE collected data. AS, JWMM, and CPB designed the study, supported data collection, and treated the patients. All authors approved the final version of the manuscript.

Conceptualization: Catharina M. Mulders-Manders, Anna Simon, and Chantal P. Bleeker-Rovers.

Data curation: Celeste Engwerda and Catharina M. Mulders-Manders.

Formal analysis: Catharina M. Mulders-Manders.

Methodology: Anna Simon, Jos W.M. van der Meer, Chantal P. Bleeker-Rovers.

Resources: Chantal P. Bleeker-Rovers, Anna Simon and Jos WM van der Meer.

Supervision: Chantal P. Bleeker-Rovers and Anna Simon.

Writing – original draft: Catharina M. Mulders-Manders, Celeste Engwerda.

Writing – review and editing: Catharina M. Mulders-Manders, Anna Simon, Jos W.M. van der Meer, Chantal P. Bleeker-Rovers.

References

[1] Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine (Baltimore) 2007;86:26–38.

[2] Mulders-Manders C, Simon A, Bleeker-Rovers C. Fever of unknown origin. Clin Med 2015;15:280–4.

[3] Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J Intern Med 2003;253:263–75.

[4] Bleeker-Rovers C, Meer JWMvd. Fever of unknown origin. Harisson's Principles of Internal Medicine. 19 ed. New York: McGraw-Hill Education; 2015.

[5] Pedersen TI, Roed C, Knudsen LS, et al. Fever of unknown origin: a retrospective study of 52 cases with evaluation of the diagnostic utility of FDG-PET/CT. Scand J Infect Dis 2012;44:18–23.

[6] Zenone T. Fever of unknown origin in adults: evaluation of 144 cases in a non-university hospital. Scand J Infect Dis 2006;38:632–8.

[7] Robine A, Hot A, Maucort-Boulch D, et al. Fever of unknown origin in the 2000s: evaluation of 103 cases over eleven years. Presse Med 2014;43:e233–40.

[8] Vanderschueren S, Del Biondo E, Ruttens D, et al. Inflammation of unknown origin versus fever of unknown origin: two of a kind. Eur J Intern Med 2009;20:415–8.

[9] Mulders-Manders C, Pietersz G, Simon A, et al. Referral of patients with fever of unknown origin to an expertise center has high diagnostic and therapeutic value. QJM 2014;110:793–801.

[10] Vanderschueren S, Eyckmans T, De Munter P, et al. Mortality in patients presenting with fever of unknown origin. Acta Clin Belg 2014;69:12–6.

[11] de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76:392–400.

[12] Knockaert DC, Vanneste LJ, Bobbaers HJ. Recurrent or episodic fever of unknown origin. Review of 45 cases and survey of the literature. Medicine (Baltimore) 1993;72:184–96.

[13] de Kleijn EM, van der Meer JW. Fever of unknown origin (FUO): report on 53 patients in a Dutch university hospital. Neth J Med 1995;47:54–60.

[14] Saltoglu N, Tasova Y, Midikli D, et al. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. J Infect 2004;48:81–5.

[15] Ali-Eldin FA, Abdelhakam SM, Ali-Eldin ZA. Clinical spectrum of fever of unknown origin among adult Egyptian patients admitted to Ain Shams University Hospitals: a hospital based study. J Egypt Soc Parasitol 2011;41:379–86.

[16] Tabak F, Mert A, Celik AD, et al. Fever of unknown origin in Turkey. Infection 2003;31:417–20.

[17] Moawad MA, Bassil H, Elsherif M, et al. Fever of unknown origin: 98 cases from Saudi Arabia. Ann Saudi Med 2010;30:289–94.

[18] Ryuko H, Otsuka F. A comprehensive analysis of 174 febrile patients admitted to Okayama University Hospital. Acta Med Okayama 2013;67:227–37.

[19] Mir T, Nabi Dhobi G, Nabi Koul A, et al. Clinical profile of classical Fever of unknown origin (FUO). Caspian J Intern Med 2014;5:35–9.

[20] Vanderschueren S, Knockaert D, Adriaenssens T, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. Arch Intern Med 2003;163:1033–41.

[21] Harrison SR, McGonagle D, Nizam S, et al. Anakinra as a diagnostic challenge and treatment option for systemic autoinflammatory disorders of undefined etiology. JCI Insight 2016;1:e86336.