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FEVER OF UNKNOWN ORIGIN: DESCRIPTIVE STUDY

Abstract

Background: fever of unknown origin is one of the diagnoses more difficult in our area, because it involves monitoring of a complex algorithm of several procedures to establish its cause and con frequently takes too long before any explanation. Therefore, the objective is to get to your diagnosis etiologic and to do a particular series of steps. **Objective:** to describe the most frequent causes of classical fever of unknown origin in the hospital setting and make a simplified diagnostic search algorithm for this pathology. **Methods:** a case-series study of 85 patients admitted to the Hospital Obispo Polanco with a diagnosis of fever of unknown origin conducted from 2013 to 2018 in the therapeutic services except for pediatrics and surgery units. The study variables included age, sex, complementary studies (variables from humoral, microbiological and biopsies), results obtained, diagnosis of each patient, treatment. **Results:** of all patients, 23 (27 %) had infections, of which 14 (16 %) of respiratory focus, 6 (7 %) of urinary focus, 2 (2 %) of abdominal focus and 1 (1 %) of the skin focus. Seven patients (8 %) had neoplasms, three of which (3 %) of respiratory origin, three of digestive tract (3 %) and one of prostatic origin (1 %). In four patients (5 %) were diagnosed of the rheumatic diseases. In 51 (60 %) patients not be could diagnose any cause of fever of unknown origin. **Conclusions:** the first cause of fever of unknown origin is diseases of unknown etiology with 60 % (51 cases) without being able to identify the clear focus. Among the known etiologies, the most private pathology is infectious bacterial diseases of the respiratory and urinary tracts (27 % — 23 patients). The third place is occupied by oncological diseases with a predominance of malignant pulmonary neoplasms (8 % — 7 patients). Rheumatological diseases occupy the last place and, in this study, accounted for only 5 % (4 patients).

Key words: *fever of unknown origin, infectious diseases, malignant tumors, algorithm of diagnostic search, treatment*

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ESR — erythrocyte sedimentation rate, HIV — human immunodeficiency virus, FUO — fever of unknown origin

Introduction

Fever of unknown origin (FUO) is a very difficult clinical «task» in the practice of many medical professionals, so it is very important to take into account a number of standardized steps that will allow you to make an etiological diagnosis of this pathology. For this reason, it is necessary to create a well-structured algorithm in order to make maximum use of the patient's hospitalization time and to identify the etiological factor as soon as possible.

In accordance with the criteria of R. B. Petersdorf and P. B. Beeson (1961), FUO was described as: repeatedly raising the temperature to 38.3 ° C for more than 3 weeks without establishing any

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diagnosis after one week of hospitalization. Subsequently, new criteria appeared by Durack and Street (1991), and currently FUO is defined as: a temperature of more than 38.3 ° C, recorded several times for more than 3 weeks, without establishing a diagnosis after 3 days of hospitalization or after 3 outpatient visits [1, 2].

This clinical syndrome is divided into four types: classical, FUO in patients with neutropenia, nosocomial type and FUO associated with infection caused by human immunodeficiency virus (HIV). There exists a huge variety of etiological causes that can cause FUO, among them there are four main groups: malignancies (Hodgkin's disease, colon cancer, pancreatic cancer), infectious processes (tuberculosis, endocarditis, cytomegalovirus, human immunodeficiency virus, intraabdominal abscesses, osteomyelitis), autoimmune and rheumatic diseases (temporal arteritis, rheumatic polymyalgia, systemic lupus erythematosus, systemic vasculitis) and other diseases (pulmonary embolism, drug fever) [1, 2, 3].

The purpose of our study was to describe the most common causes of FUO in inpatient conditions (the classic type of FUO), taking as a representative sample the cases diagnosed in the Obispo Polanco hospital over the previous 5 years (2013-2018); and, as a consequence, establish a single clinical diagnostic algorithm for the optimal use of additional examination methods.

Materials and methods

A descriptive study of a series of cases with 85 inpatients with a diagnosis of FUO at the hospital «Obispo Polanco» located in therapeutic departments, with the exception of the pediatric department and general surgery, was conducted during 5 years, in the period: March 2013 to August 2018.

Inclusion criteria: the study included patients aged over 18 years, male and female, with fever over 38.3 ° C and higher, lasting more than three weeks and hospitalized for more than one week without establishing the cause of the febrile syndrome.

Exclusion criteria: immunosuppressive patients were excluded from the study (with neutropenia — leukocytes less than 1000 / ml or neutrophils less than 500 / μl; HIV infection; hypogammaglobulinemia with IgG less than 50% of the norm (<7 g / l); being treated with prednisone or its equivalent for more than 2 weeks) and patients with a pre-established diagnosis of malignant neoplasm.

Clinical histories and discharge records of each patient were reviewed using the following collected data: age, gender, axillary temperature, symptoms accompanying febrile syndrome, additional laboratory and instrumental diagnostic methods performed, established diagnosis and treatment applied in each case.

All data was collected in an Excel document to create a single database with the percentage of each pathology that could cause a classic type of fever of unknown origin.

Results and discussion

According to the obtained results, the first step of specialists after conducting a thorough physical examination was the appointment of additional methods of laboratory diagnosis. Complete blood count with the determination of erythrocyte sedimentation rate (ESR), biochemical blood analysis, including C-reactive protein and procalcitonin, coagulogram and urinalysis.

Also, at the first stage of the survey, a microbiological analysis of blood, urine and feces, a Clostridium difficile toxin determination in the case of diarrhea syndrome, a human immunodeficiency virus serological test, antibodies to hepatitis B and C, serological tests for the detection of atypical pneumonia, brucellosis, toxoplasmosis, Epstein-Barr virus, mycoplasma, Q fever, chlamydia, Varicella Zoster virus, pneumococcal infection antigens and Legionella in the urine; in exceptional cases, in accordance with clinical suspicions, a microbiological analysis of nasopharyngeal aspirate and the thick drop method were prescribed.

The second stage, after the previous tests, was the expansion of the clinical examination by performing: the Mantoux test, chest X-ray, echocardiogram and abdominal ultrasound.

In the absence of a clinically significant result, additional invasive research methods were conducted, such as: gastroscopy, colonoscopy, bronchoscopy with biopsy, as well as computerized axial tomography of systems and organs, with possible involvement in the pathological process of FUO. After establishing the etiological diagnosis and discharge from the hospital, each patient underwent outpatient examination to further control the absence of fever and side effects of the prescribed treatment during the transition from intravenous antibacterial drugs when hospitalized for oral administration at discharge, and in the case of positive control, patients are observed annually in case of reappearance of symptoms. In the case of patients with an unspecified cause of FUO, at subsequent outpatient consultations, were observed additional new symptoms, full numbers were normalized in case of discharge with subfebrile body temperature, repeated physical examination, the effectiveness of empirical treatment and, if necessary, its correction in order to detect diagnostic prompts in the search possible etiology.

A total of 85 patients were studied, over the age of 18 years. The average age of all patients included in the study was 73 years, with a predominance of male — 59 patients (69%) and 26 patients (31%) of female sex.

The first etiological cause of FUO was infectious diseases in the case of 23 patients (27%), most of them of bacterial origin. In this group, fourteen patients with respiratory tract infections (16%) were identified, among whom five were confirmed using additional studies at the time of hospitalization and nine patients with clinical symptoms of respiratory tract infection, but with negative laboratory and instrumental methods at the time of hospitalization and confirmed later on outpatient consultation. In the latter case, these patients were given the diagnosis «Possible infectious focus of the respiratory tract» with suspicion of this type of infection due to the presence of clinical symptoms, but the inability to confirm it due to the negative result of additional studies.

In the case of six patients, urinary tract infections were detected (7%): in four patients this infectious focus was confirmed at the time of hospitalization in the inpatient unit, whereas in the case of the other two patients, symptoms of this type of infection were recorded, but with a negative result of additional laboratory tests, however, later the diagnosis was confirmed at the outpatient consultation, so they were assigned the diagnosis «Possible infectious focus of urinary tract» at the time of discharge. This group of patients is not included in the group «Unknown reasons of FUO», as this study is aimed at identifying the causes of febrile syndrome in a hospital, at the time of hospitalization of the patient, without taking into account the diagnoses established in the outpatient setting.

In the case of two patients (2%), infectious focus of the abdominal cavity were diagnosed with infectious gastroenteritis, confirmed on the basis of a clinical picture of diarrheal syndrome with pathological impurities and positive bacteriological examination of feces. Only in one case (1 %) was an infectious lesion of the skin in a patient with diabetes mellitus. Pulmonary tuberculosis was diagnosed in one patient (1%) using a Mantoux test and polymerase chain reaction for Mycobacterium tuberculosis with a positive result. The most frequent symptoms presented in this group were general deterioration, chills, shortness of breath, and dry cough.

The second reason underlying of FUO was malignant neoplasms in 7 patients (8%). In all cases, cancer tumors were diagnosed at a late stage. The following most common symptoms have been reported: asthenia, weight loss, shortness of breath, diarrheal syndrome with pathological impurities, such as blood and mucus.

Third place in the group of etiological factors took rheumatological diseases such as temporal arteritis,

systemic lupus erythematosus and rheumatic polymyalgia. The symptoms that represented the majority of patients in this etiological group were arthromyalgia, general stiffness, skin rash, pain at the level of the shoulder and pelvic girdle.

In 51 patients (61%) it was impossible to determine the etiological pathology of FUO even after a thorough physical examination to determine the morphological elements of the skin rash, damage to the oral mucosa, enlarged lymph nodes, enlarged thyroid gland, hepatomegaly and splenomegaly, cardiac murmurs, and rectal pathology manual study. In the absence of pathological signs, a complete algorithm of additional laboratory and instrumental examination methods (presented in Appendix 1 of this document), such as a complete blood count, ESR, urinalysis, biochemical blood count, C-reactive protein, proteinogram, ANA antibodies, anti-DNA, ANCA, rheumatoid factor, microbiological analysis of blood and urine, serological examinations for the presence of brucellosis, measles, toxoplasmosis, syphilis, cytomegalovirus, Epstein-virus, herpes simplex virus and Varicella Zoster, hepatitis B, C and A, HIV infection, Q fever, Legionella and Neumococo antigens in the urine, Mantoux test, electrocardiogram, chest X-ray, abdominal cavity (in 100 % of cases), negative results of which were repeated physical examination, ultrasound examination of the abdominal cavity, computed tomography (in the case of 41 patients), gastroscopy and colonoscopy, biopsy of the temporal artery (in the case of 32 patients in this group) — Table 1, Table 2, Diagram 1.

Patients in this group of descriptive studies observed a duration of febrile syndrome of more than 3 weeks before hospitalization (maximum duration of 2 months) and more than three days during their stay in hospital (as an important FUO criterion for inclusion in this study). In the case of 41 patients of this etiological group, the maximum duration of the febrile syndrome was 4 weeks, whereas in 10 patients the normalization of body temperature figures fell at the end of the first week — the beginning of the second week of hospitalization.

Table 1. *Distribution of etiological causes of FUO in relation to the total number of cases*

Etiological causes	Number of cases	Percentage (%)
Infectious diseases	23	27
Malignant neoplasms	7	8
Rheumatological diseases	4	5
Unknown reasons	51	60
Total number of cases	**85**	**100**

Note: FUO — fever of unknown origin

Table 2. *The distribution of etiological factors of FUO by diagnostic groups*

Diagnostic group	Number of cases
Infectious diseases	**23**
– Community-acquired pneumonia	**2**
– Bronchitis	**2**
– Pharyngitis	**1**
– Tuberculosis	**1**
– Confirmed urinary tract infection	**2**
– Intra-abdominal infection	**2**
– Possible infectious focus of the respiratory tract	**9**
– Possible infectious focus of urinary tract	**4**
Malignant neoplasms	**7**
– Pulmonary adenocarcinoma	**3**
– Adenocarcinoma of the colon	**2**
– Pancreatic adenocarcinoma	**1**
– Adenocarcinoma of the prostate gland	**1**
Rheumatological diseases	**4**
– Temporal arteritis	**2**
– Systemic lupus erythematosus	**1**
– Rheumatic polymyalgia	**1**
Without diagnosis	**51**
Total number of cases	**85**

Note: FUO — fever of unknown origin

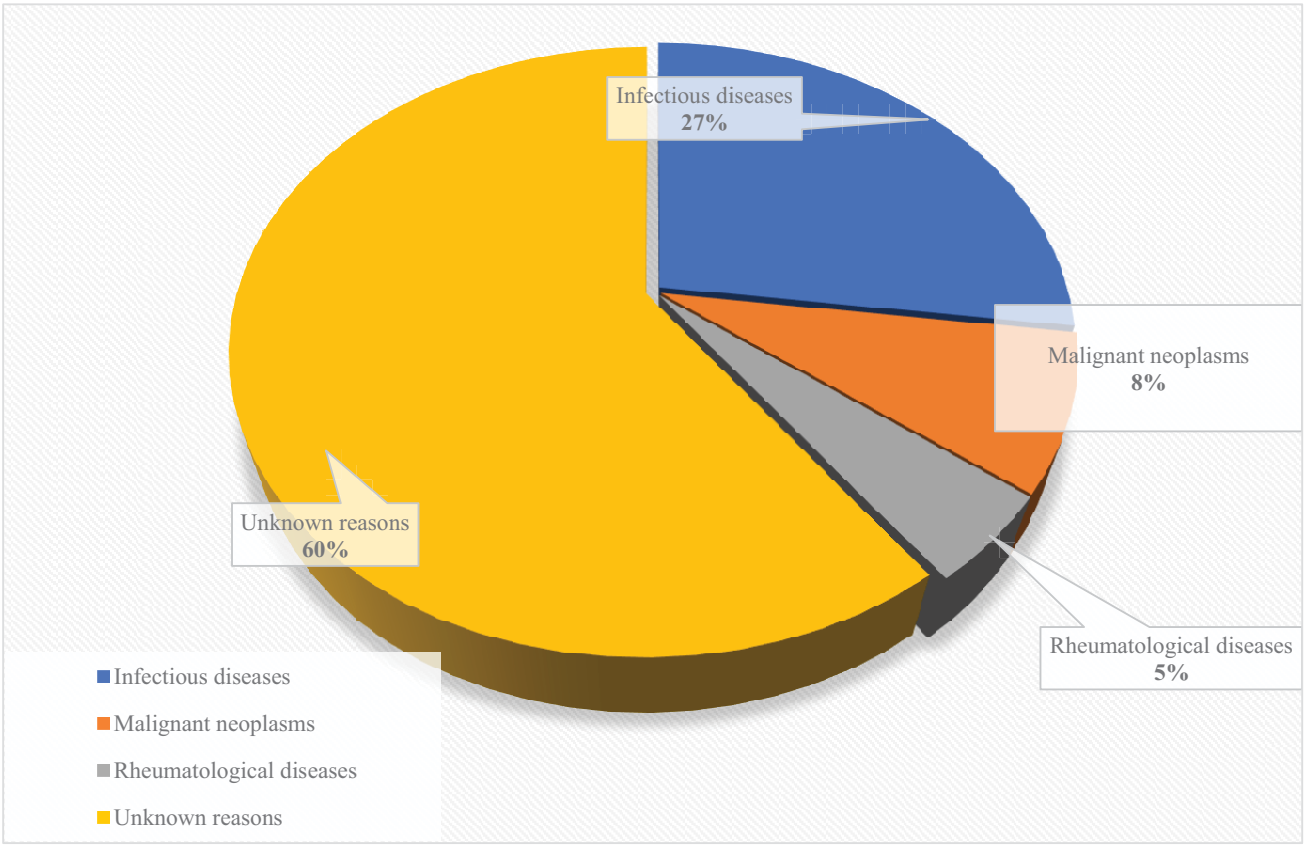


Diagram 1. *Distribution of etiological factors of FUO among the total number of cases*

Note: FUO — fever of unknown origin

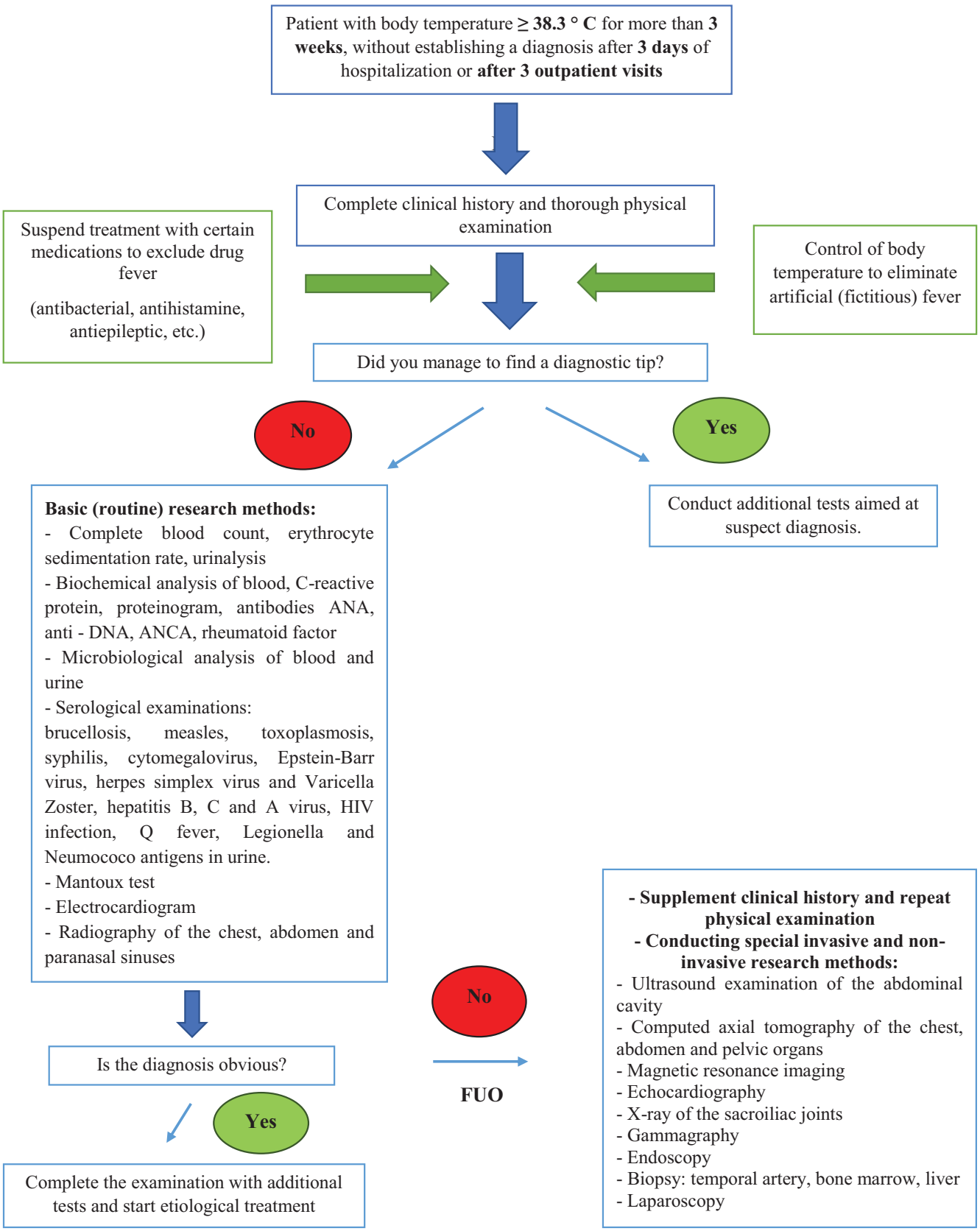
At discharge, the following diagnoses were assigned to patients of this group: «Fever of unknown origin» (in case of 28 patients — 54% of this group), «Feverish syndrome» (3 patients — 6 %), «Fever without visible focus of infection» (in the case of 10 patients — 20%) if after conducting a complete diagnostic search and empirical treatment, it was not possible to establish the etiological cause and patients with improved general condition at the time of discharge from the inpatient department still retained non-normalized temperature figures of subfebrile temperature — 37, 4 -37, 6°C (41 patients in this group).

Patients with complete absence of symptoms and normalization of body temperature were discharged with diagnoses «Feverish syndrome resolved without treatment» (3 patients — 6%) and «Fever of unknown origin with good response to antibacterial treatment» (in case of 7 patients — 14%).

It was noted that irregularities in the indicators of the general analysis of blood and ESR were most often identified. Conversely, a series of tests that most often gave negative results in almost all cases, were microbiological analysis of nasopharyngeal aspirate, feces and thick drop method for the determination of malarial plasmodium.

During treatment with antibacterial therapy, medical specialists preferred to start with a group of third or fourth generation cephalosporins, followed by penicillin derivatives or fluoroquinolones. If first-line antibacterial drugs did not lead to clinical improvement of the patient's condition, treatment with broad-spectrum antibiotics was applied: from the group of beta-lactam antibiotics, such as imipenem or meropenem and linezolidide from the oxazolidinone group.

As a result of this study, it was found that infectious diseases are the most frequent etiological cause



Appendix 1. *The diagnostic search algorithm for the etiological cause of FUO, developed in the hospital "Obispo Polanco" and used in this study*

Note: ANA — antinuclear antibodies, ANCA — antineutrophil cytoplasmic antibodies, HIV — human immunodeficiency virus, anti-DNA — anti-double stranded DNA antibodies, FUO — fever of unknown origin

underlying the classical type of FUO, which corresponds to the medical literature analyzed for this clinical syndrome [3, 4, 5]. Malignant neoplasms continue to occupy the second place and it should be noted that in this study, cancer of the respiratory tract and the digestive tract predominate, that disagrees with the majority of the reviewed studies, the results of which in this etiological group are dominated by neoplastic diseases of the blood and lymph.

In order to establish the etiological diagnosis of FUO, it is necessary to adhere to a certain diagnostic search algorithm. So far, there are several diagnostic algorithms for FUO, but only a few of them have been confirmed by prospective studies [6], so an individualized approach to each individual patient and a targeted examination are necessary to avoid unnecessary additional research methods. Clinical history and physical examination of patients should be exhaustive and it is a fundamental step in the diagnostic search for FUO. However, despite the systematic approach to the diagnosis of this pathology, in most cases the etiological cause of FUO remains unknown, which shows this study in 61% of all patients (51 patients).

Conclusions

Thus, a fever of unknown origin is a syndrome of complex clinical management, which requires a strictly organized plan of action on the part of medical specialists, which allows to establish a possible cause in the shortest possible time and begin etiological treatment.

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

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