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*Original Article*

## Fever of Unknown Origin in Renal Patients

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### Abstract

**Background.** Fever of unknown origin is always a diagnostic challenge. In adult nephrology, the common causes of fever of unknown origin are infections, autoimmune diseases and occult malignancies. We should keep in mind that as the duration of fever increases, the likelihood of infectious causes decreases.

**Methods.** We tried to explain 45 cases of prolonged sub febrile states in patients (female 38, male 7, aged 19-64 years, mean age  $36\pm 17.8$  years) who referred to the nephrologic outpatient clinic from 2000-2005. To find sources of occult fever, we used many diagnostic maneuvers, such as microbiologic and immunologic tools, tests of autoimmunity (ANA, aDNA, RF etc), ultrasonography, computed tomography, chest and another x-rays.

**Results.** In our patients, bacterial infections remain the leading cause, i.e. uro-genital tuberculosis in 18 cases, and one of chronic prostatitis. Viral infections (Coxsackie's B) with chronic fatigue syndrome were diagnosed in 2 cases. Undiagnosed sub febrile states accounted in 22 patients, autoimmune diseases were found in 16 patients (primary Sjögren's syndrome in 9, Hashimoto's thyroiditis in 6 and systemic vasculitis in one) and 6 patients have been autoimmune diseases suspected, but still not confirmed. Treatment of Sjögren's syndrome caused normalization of the body temperature. We discovered two malignancies (bladder carcinoma and Hodgkin's disease).

**Conclusions.** With improved noninvasive and microbiologic techniques, most cases of sub febrile state in nephrology are found to be caused by uro-genital tuberculosis as well as autoimmune systemic diseases.

**Keywords:** autoimmune systemic disease; Hashimoto's thyroiditis; Sjögren's syndrome; sub-febrile state, urogenital tuberculosis

### Introduction

Substances that cause fever are called pyrogens, and may be either exogenous or endogenous. The majority of exogenous pyrogens are microorganisms, their products or toxins. Many endogenous products result in the release of endogenous pyrogens, thereby causing fever. A classification of fever of unknown origin (FUO) includes: classic FUO, nosocomial FUO

(in hospitalized patients), neutropenic FUO and HIV-associated FUO. Classic FUO includes infections, malignancy, inflammatory diseases, drug fever etc. Fever of unknown origin is always a diagnostic challenge. In adult nephrology, the common causes of FUO are infections, autoimmune diseases and occult malignancies. We should keep in mind that as the duration of fever increases, the likelihood of infectious cause decreases [1]. Importantly, the incidence of tuberculosis is increasing worldwide, especially in Serbia in the last two decades [2,3].

### Patients and methods

The purpose of this retrospective trial was to evaluate 45 cases of prolonged sub febrile states in patients who referred to the renal outpatient clinic from year 2000 - 2005 with abnormal urinalysis (pyuria, microhematuria, non-nephrotic proteinuria) and sub febrile state longer than 6 months. The group consisted of 38 female patients and 7 males. The patients aged 19-64 years, mean age was  $36\pm 17.8$  years. To find the source of occult fever, we used many diagnostic maneuvers: microbiologic (cultures, Löwenstein, PCR), immunologic tools (immunoelectrophoresis of serum and urine, complement fractions etc), tests of autoimmunity ANA, aDNA, ANCA, RF), ultrasonography (abdomen, neck etc), x-rays: chest, intravenous pyelography etc, computed tomography, NMR.

### Results

The sub febrile patients were observed 6-12 months until specifying the diagnosis. Urinary infections remain the leading cause, such as uro-genital tuberculosis and chronic prostatitis. We found 18 patients to have positive Polymerase Chain Reaction - PCR samples (urine, sperma) on Mycobacterium tuberculosis, however half of patients were Löwenstein positive. Viral infections (Coxsackie's B) with chronic fatigue syndrome were the only reasons found in two patients. Tests of autoimmunity and immunologic tools confirmed autoimmune systemic diseases in 16 patients (Sjögren's syndrome, Hashimoto's thyroiditis and systemic vasculitis). In two patients sub febrile state was a part of the paraneoplastic syndrome because of malignancies (bladder carcinoma and Hodgkin's disease). Undiagnosed sub febrile states account for 6 patients who have been autoimmune diseases suspected, but still not confirmed.

**Table 1.** Causes of sub febrile states in 45 renal patients

	Diagnosis	Number of patients	%
1.	Uro-genital tuberculosis	18	40 %
2.	Chronic prostatitis	1	2,2 %
3.	Viral infections	2	4,4 %
4.	Sjögren's syndrome	9	20 %
5.	Hashimoto's thyroiditis	6	13,3, %
6.	Systemic vasculitis	1	2,2%
7.	Paraneoplastic syndrome	2	4,4 %
8.	Undiagnosed FUO	6	13,3 %

## Discussion

In adults, the common causes of sub febrile states are infections, autoimmune systemic diseases and occult malignancies. We tried to explain causes of 45 cases of prolonged sub febrile states (duration longer than 6 months) followed in a period from 2000-2005. Infections remain the leading cause of FUO in 46,6 % of patients (uro-genital tuberculosis in 18 and chronic prostatitis in one case). It might be partially explained by poorer living conditions and emotional stress imposed by the economic sanction in the period of 1992-1994 and the succeeded war in 1999, as well as by the great number of refugees from Bosnia, Croatia and Kosovo. All of these factors could have promoted the tuberculous infection in Serbia [4,5]. The current golden standard for the diagnosis of tuberculosis, detection of mycobacterial growth on conventional Löwenstein-Jensen medium, requires 6 to 8 weeks, and detection is largely dependent upon the number of organisms in the inoculum. Newer and more specific molecular biologic techniques are constantly being developed and may prove to be helpful diagnostic techniques. More rapid diagnostic tests detect nucleic acids of *Mycobacterium tuberculosis*. Polymerase Chain Reaction- PCR is simple, fast, highly sensitive and specific method which enables to identify even the least quantities of bacteria in urine, sperma or any other biological sample, and enables diagnosis in incipient stadium of the disease. Treatment of uro-genital tuberculosis by antituberculous drugs for 6-12 months was successful in all patients. In addition, autoimmune rheumatic diseases were found in 35,5% of patients [6]. Treatment of Sjögren's syndrome caused the normalization of body temperature [7]. Further-

more, the abnormal urinalysis was frequently explained by an aerobic fecal flora urinary infections or *Chlamydia trachomatis* and / or *Ureaplasma urealyticum* infections [8].

We discovered two malignancies. Treatment of malignancies was surgical (bladder carcinoma) or conservative (Hodgkin's disease). Undiagnosed FUOs account for approximately 13 percent, six patients were collagenosis suspected, but still not diagnosed.

## Conclusions

With improved noninvasive and microbiologic techniques, most cases of sub febrile state in our patients are found to be caused by uro-genital tuberculosis as well as autoimmune systemic diseases.

*Conflict of interest statement.* None declared.

## References

1. Stanojic A, Radmilovic A. Fever of unknown origin in nephrology. *Third BANTAO Congress*, Belgrade, September 18-20, 1998, Book of Abstracts, p 56.
2. Raviglione MR, Snider DE, Kochi A. Global epidemiology of tuberculosis-morbidity and mortality of a worldwide epidemic. *JAMA* 1995; 273: 220-226.
3. Mehta J.B., Dutt A, Harvil L and Mathews K.M. Epidemiology of extrapulmonary tuberculosis, *Chest*, 1998; 34-38.
4. Stanojic A, Radic O. Rapid diagnosis of renal tuberculosis by means of PCR in Serbia and Montenegro. 5<sup>th</sup> European Congress of Chemotherapy and Infection, 17-20.October 2003, Rhodes, Abstract Book 45.
5. Micic S. Tuberkuloza bubrega. *Medicinska istrazivanja*, vol. 35 (3) 2001, 54.
6. Stojanovich L, Milovanovich B, de Luka SR *et al.* Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren syndrome and other autoimmune diseases. *Lupus* 2007; 16: 1-5.
7. Vitali C, Bombardieri S, Moutsopoulos HM *et al.* Preliminary criteria for the classification of Sjögren's syndrome, results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993; 36: 340-347.
8. Stanojic A, Radmilovic A, Cacic Z. The frequency of sexually transmitted diseases among urinary tract infections. *XXXV Congress of the EDTA*, Rimini, 1998; A174.