

## Some Aspects of Urogenital Tuberculosis

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### Abstract

**Background and Aims:** Urogenital tuberculosis (UGT) is a worldwide disease with non-typical and misleading clinical features, resulted in late diagnosis. Late diagnosed complicated forms of renal tuberculosis (TB) are poor for standard chemotherapy, the additional pathogenetic therapy is necessary. The aims of the current study were to estimate the epidemiological situation on UGT in the region with high incidence rate and to value the efficiency of the complex etiopathogenetic therapy for bladder TB.

**Methods:** Estimates of extrapulmonary tuberculosis incidence and its structure in Siberia have been made on the basis of the data available in official reporting forms No 8 (approved by Resolution No 175 of the Russian Statistics Agency 11 November, 2005).

In addition, 102 patients with bladder TB were enrolled in study: 76 were treated with standard tetrad (isoniazid + streptomycin + pyrazinamid + rifampicin), and 26 received modified tetrad in combination with tropium chloride.

**Results:** During the last 5 years the incidence of TB maintains stable high in Siberia, and in 2008 it raised up to 139.6 per 100000 habitants. UGT was the prevalent form (46.0 – 33.5%); TB of bone and joints was in the second place (20.1 – 32.7%), this was followed by lymphonodal TB (14.7 – 14.9%).

Standard chemotherapy had poor efficiency for bladder TB: only 42.1% could be cured, 57.9% developed complications such as posttuberculous cystalgia (36.8%) and microcystis (21.1%). In patients received the combined treatment outcome was favourable: urinary frequency reduced about 75%, bladder capacity increased an average of 4.7 fold. None of these patients developed true microcystis.

**Conclusions:** In Siberia, there is an epidemic of TB. UGT is the most common form among extrapulmonary TB. Standard chemotherapy for bladder TB demonstrated poor results, but combination chemodrug plus tropium chloride was more effective and should be recommended to all patients with bladder TB grade 2-3.

**Keywords:** Urogenital Tuberculosis, Mycobacterium Tuberculosis, Diagnosis, Antituberculous Chemotherapy, Epidemiology

### Introduction

The World Health Organization (WHO) recognized tuberculosis (TB) as a global problem and emphasizes, that TB kills more young and adults than any other infectious disease; TB kills more women than any single cause of maternal mortality (1). Although TB is very old disease (first signs are dated of time of pharaohs), it is not absolutely clear still now.

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Received: 11 May 2009  
Revised: 30 Jul 2009  
Accepted: 5 Aug 2009

Most controversies are concerning extrapulmonary TB, particularly, urogenital TB. There is an opinion that patients with urogenital tuberculosis (UGT) in developed countries have fewer specific symptoms and lower rates of delayed diagnoses compared with patients from other countries (2). Unfortunately, UGT has no specific symptoms at all, and it is a reason for late diagnosis both in poor and rich countries. UGT raises major diagnostic problems due to the frequently atypical and misleading clinical features(3). Flank pain and non-specific urinary complaints are the major symptoms of UGT(4). Patients usually exhibit local symptoms; irritative symptoms were in 47.3%. Fever, weight loss and anorexia were uncommon (3, 5-6). It was found that latent period between infection with *Mycobacteria tuberculosis* (MBT) and the expression of UGT may be 20 years or more (7). The most common abnormalities were pyuria and gross hematuria(3, 6). The isolation of MBT from urine was obtained in 1961-1972 years in 80% (7), now it is less often due to widespread use of strong antibacterials in general clinics, especially fluorquinolons. In the year 2000, urine culture was positive for TB in 57% (3) and even 5.2% (6).

In spite of all efforts TB maintains its epidemic level in Siberia - 66% of all Russian territory (8). Although pulmonary TB is thought to be more dangerous, extrapulmonary TB is also contagious and potentially lethal. In addition, extrapulmonary TB affects the quality of life much more than pulmonary TB. Bladder TB is one of the most serious complications of renal TB, and it is diagnosed in 45.6% - 54% among UGT (3, 9).

Tuberculous cystitis can be classified as following (10):

Grade 1- Infiltrative form - tubercle

Grade 2- Ulcerous form - erosive

Grade 3- Spastic cystitis (false microcystis) actually overactive bladders (OAB)

Grade 4- True microcystis, up to full shrinkage of the bladder

These forms can either develop in an aggressive manner or can develop gradually by going through intermediate grades.

The first 2 grades can be treated conservatively. The 4th grade demands surgical intervention - enterocystoplasty. Spastic microcystis is a transition stage inclined to transform to true microcystis, causing a significant decrease in the quality of life of the affected person. Thus the treatment of TB cystitis in its early stages is very important.

The aims of the current study were to estimate the epidemiological situation on UGT in the region with high incidence rate and to value the efficiency of the complex etiopathogenetic therapy for bladder TB.

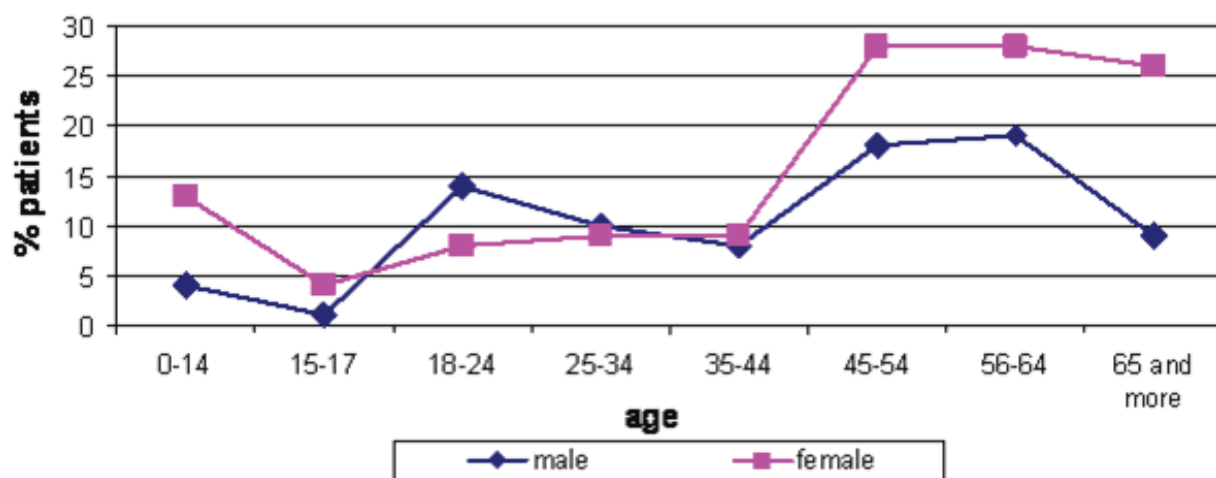
## Materials and Methods

Estimates of extrapulmonary tuberculosis incidence and its structure in Siberia have been made on the basis of the data available in official reporting forms No 8 (approved by Resolution No 175 of the Russian Statistics Agency 11 November, 2005). Statistical reports from 21 regions from Siberia (66% of Russian Federation) were revised annually to reflect new information gathered through surveillance (case notifications) and from special studies.

Also 102 patients with bladder TB were enrolled in study. We have investigated the outcome of the standard TB pharmacotherapy – the tetrad (isoniazid 10 mg/kg + rifampicin 10 mg/kg + pyrazinamid 20 mg/kg + streptomycin 15 mg/kg) in the 1st group of 76 patients (30 men and 46 women) having the first 3 grades of tuberculous cystitis. In addition, we followed the progression of a second group of 26 patients (23 women and 3 men) with an active bladder TB grade 3 (spastic microcystis). The age range was 25 - 67 years. Seventeen of them had also unilateral tuberculous papillitis and 9 had cavernous renal tuberculosis.

The clinical workup of the patients in both groups included: urinalysis, bacteriological investigation of 3-5 consecutive early morning specimens of urine,

### Incidence of UGT in defferent age groups



**Diagram 1.** Incidence of UGT in different age groups

plain X-ray of the renal areas and the bladder to detect calcifications, intravenous urography, retrograde urethrography (when indicated), ultrasound investigation of the urinary tract, cystoscopy with bladder biopsies and uroflowmetry. For patients with tuberculous cystitis grades 3-4 – also cystography was performed.

All patients with active bladder TB (second group) received the “modified” tetrad (with isoniazid 10 mg/kg + rifampicin 10 mg/kg + pyrazinamid 20 mg/kg + ofloxacin 800 mg) simultaneously during 2 months. This was followed by a 6-10 months treatment with isoniazid and rifampicin only. Streptomycin was removed from the standard tetrad, because the use of streptomycin potentially leads to the formation of fibrous tissue in the bladder wall and may accelerate the development of microcystis. In addition, from the first day of the therapy, all patients received trospium chloride 15 mg twice a day during three months as pathogenetic treatment.

### Results

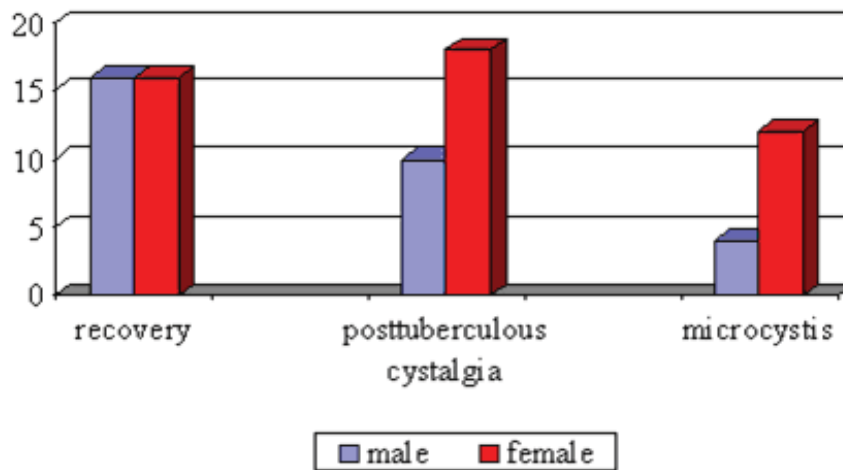
During the last 5 years the incidence of TB maintains stable high in Siberia (126.1 per 100000

habitants in 2003 and 128.8 in 2007), but in 2008 the incidence increased up to 139.6 per 100000 habitants. However, during the same period the incidence of extrapulmonary forms decreased from 4.3 to 3.2 per 100000. In 2003, 1078 new patients with extrapulmonary TB were diagnosed in Siberia; and only 863 new patients in 2008. The proportion of clinical forms was identical throughout these years: Urogenital TB was the prevalent form (46.0 – 33.5%); TB of bone and joints was in the second place (20.1 – 32.7%), this was followed by lymphonodal TB (14.7 – 14.9%).

In Siberia, in the year 2008, 208 patients got sick with UGT (excluding 92 women with gynecological TB), male 39.1% and female 60.1%. In addition, there were 13 children younger than 14 years of age and 4 teenagers between 15-17 years (Diagram 1).

The outcome analysis of patients in the first group showed that standard therapy is insufficient in more than a half of the cases. With this treatment, only 32 patients (42.1%) could be cured. Forty four patients (57.9%) developed complications such as post-tuberculous cystalgia (28 patients – 36.8%) and microcystis (16 patients – 21.1%). Incontinence developed in 8 patients (19.1%): three women

**Outcomes of bladder TB in 1st group (30 male and 46 female)**

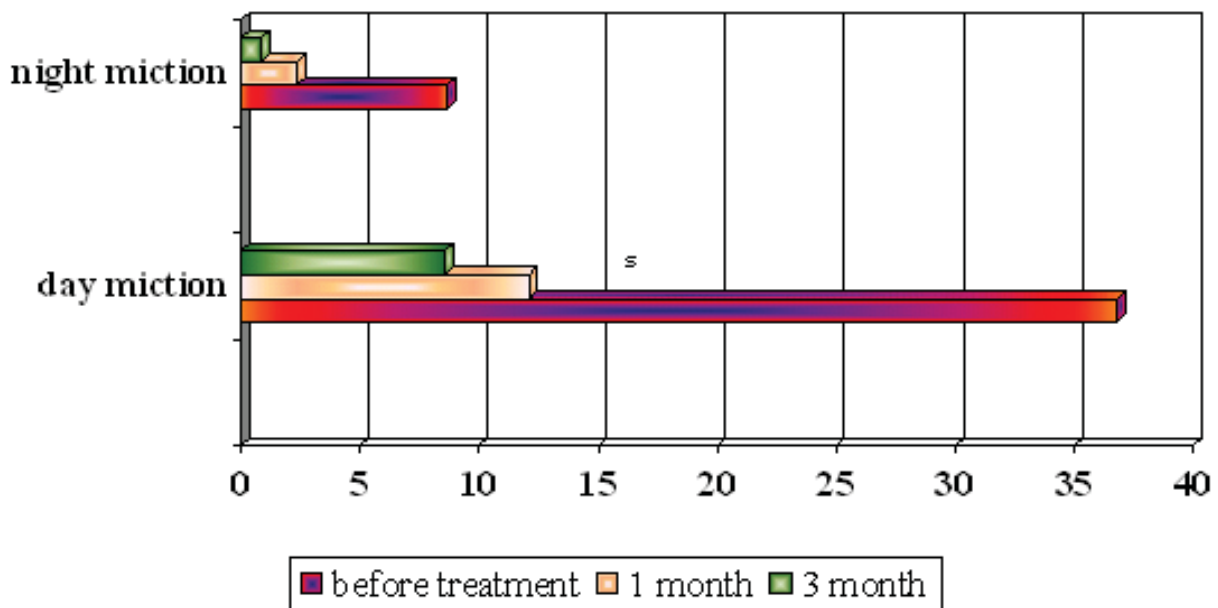


**Diagram 2.** Outcomes of bladder TB in 1st group (30 male and 46 female)

(average age 60.3 years) and five men (average age 66.4 years). All of these patients had bilateral cavernous renal tuberculosis; in addition all the male patients in this group developed tuberculosis of the prostate.

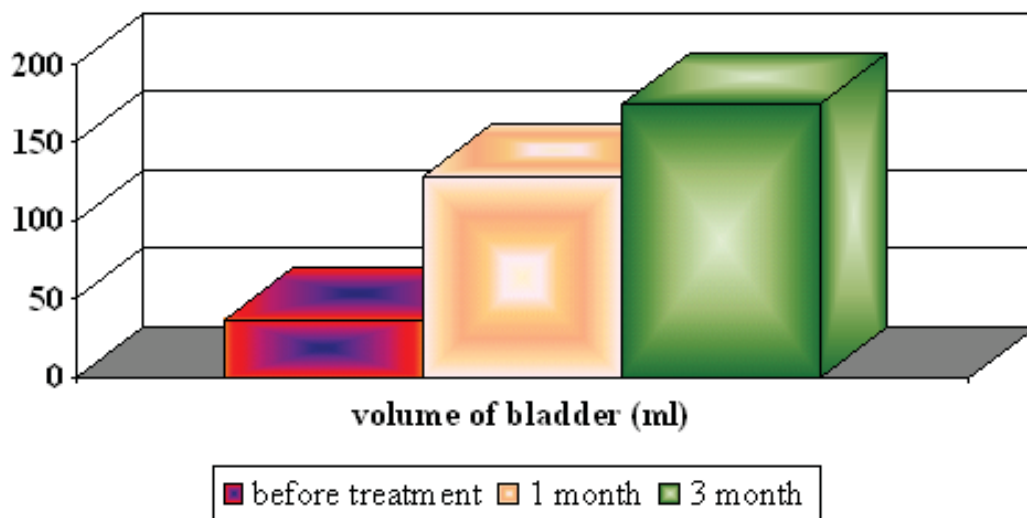
There were differences in the outcomes of bladder TB between men and women (Diagram 2). When given the standard tetrad 53.4% of men and 34.8% of women could be cured. In 33.6% of men and in 39.1% of women tuberculous cystitis resulted in

**Dynamic of voiding frequency (n=26)**



**Diagram 3.** Dynamic of voiding frequency (n=26)

### Dynamic of bladder capacity (n=26)



**Diagram 4.** Dynamic of bladder capacity (n=26)

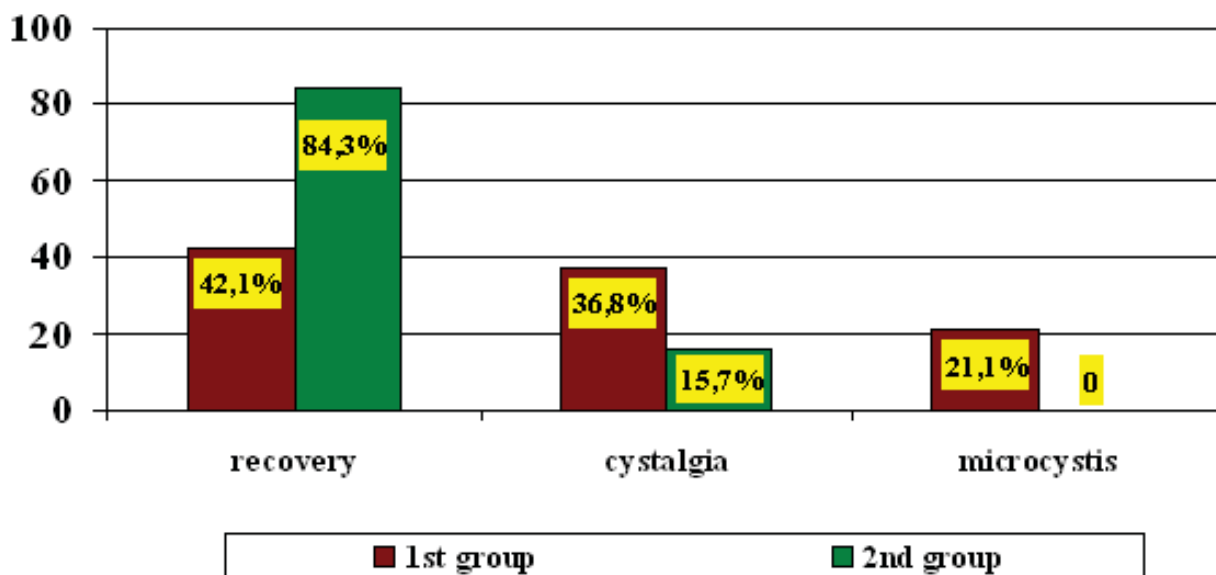
post-tuberculous cystalgia and in 13.3% of men and 26.1% of women the microcystis developed.

The 26 patients with tuberculous cystitis Grade 3 in a second group received alongside with the modified “tetrad” also pathogenetic treatment with trospium chloride.

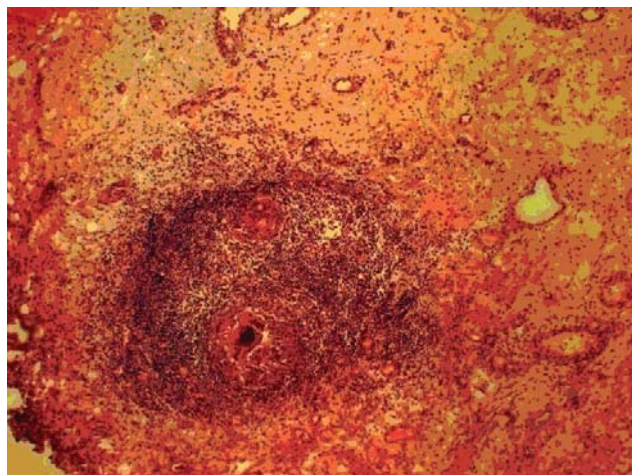
We observed that this group of patients responded in a favourable manner to the combined treatment: decrease in dysuria, increase in the capacity of the bladder (Diagrams 3 and 4).

These results show that the frequency of mictions and bladder capacity started to change during the first

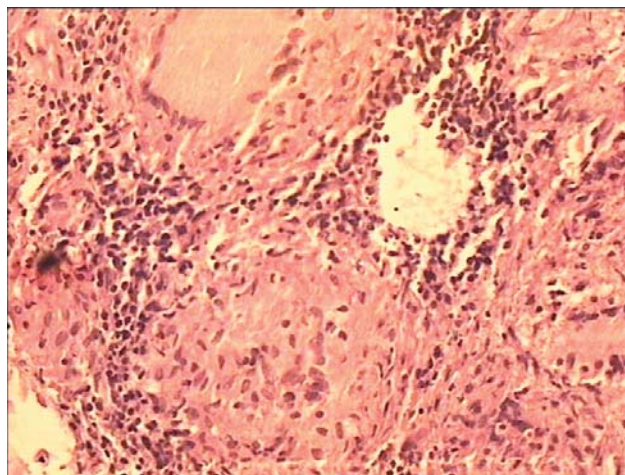
### Comparison of outcomes of bladder TB



**Diagram 5.** Comparison of outcomes of bladder TB



**Figure 1.** Bladder TB, Epithelioid-cell granulomata with giant cells, surrounded by wide zone of lymphoid infiltration. X100, Hematoxylin and eosin



**Figure 2.** TB of bladder, Epithelioid-cell granulomata with giant cells within muscular layer of the bladder X400 Hematoxylin and eosin

month of the treatment. Then the change continued but it became slower. The outcome of the treatment of this group of patients is summarized in a Table 1.

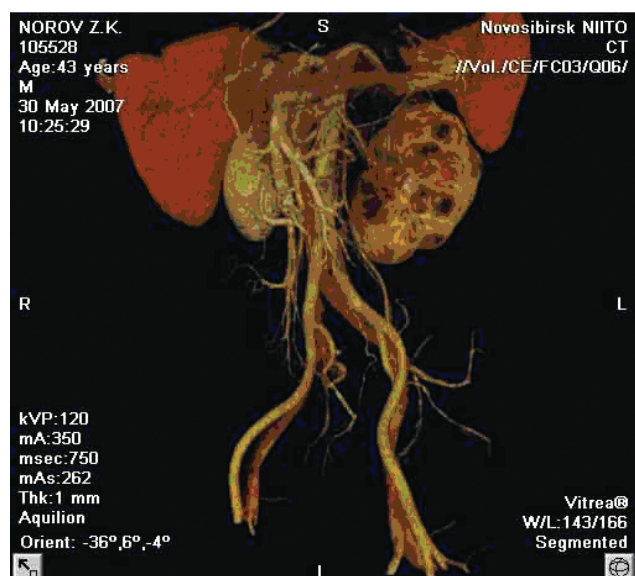
In all these patients the outcome of the treatment was favourable: urinary frequency reduced about 75%, bladder capacity increased an average of 4.7 fold. None of the patients developed true microcystitis after the combined treatment. However, after standard treatment this complication developed in 21.1% of the patients. Tolerance to the treatment was good: only one patient had minor side effects (mouth

dryness). Comparison of the results of the therapy in both groups is demonstrated by Diagram 5.

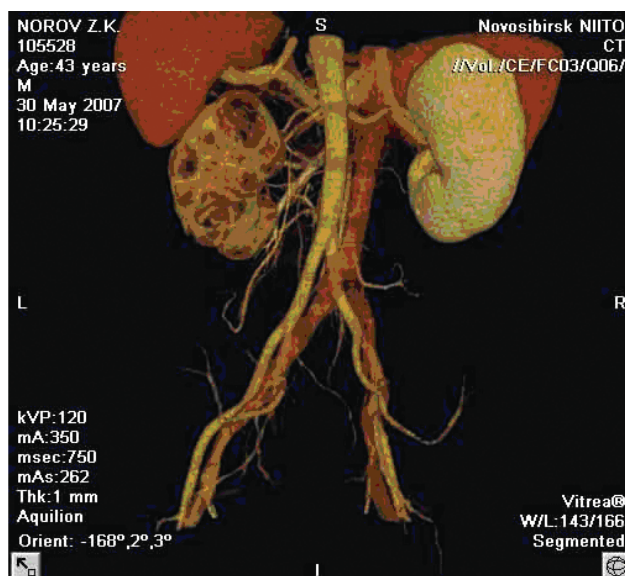
Some cases below show difficulties in the diagnostic and the therapy of bladder TB

Case 1: Patient C., female 54 years, applied with hematuria, frequent and painful urination. To rule out bladder cancer the patient underwent a cystoscopy, but the source of the bleeding could not be identified. Bladder biopsy showed tuberculosis (Fig.1).

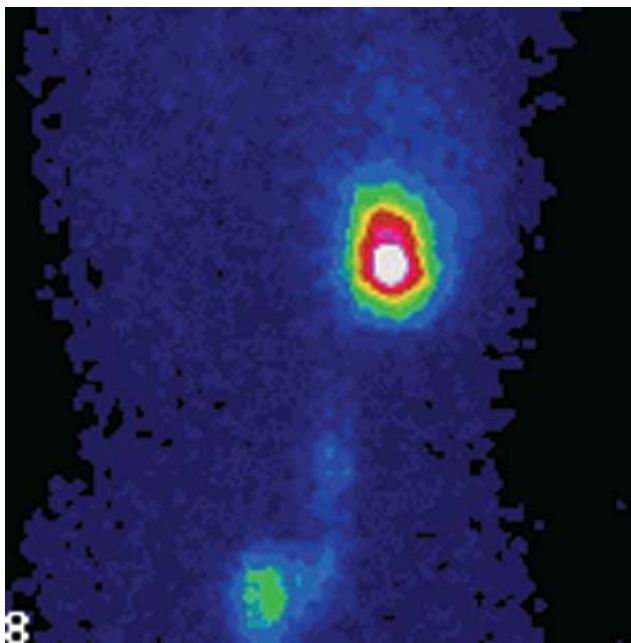
Case 2: Patient E. male, 49 years, applied with



**Figure 3.** Spiral computer tomogram of the same kidney, posterior view



**Figure 4.** Spiral computer tomogram of the same kidney anterior view



**Figure 5.** Radioisotopic scintigramm

a history of moderate dysuria during the last year. Cystoscopy showed bladder edema and contact hemorrhage. Bladder biopsy showed tuberculosis (Fig.2).

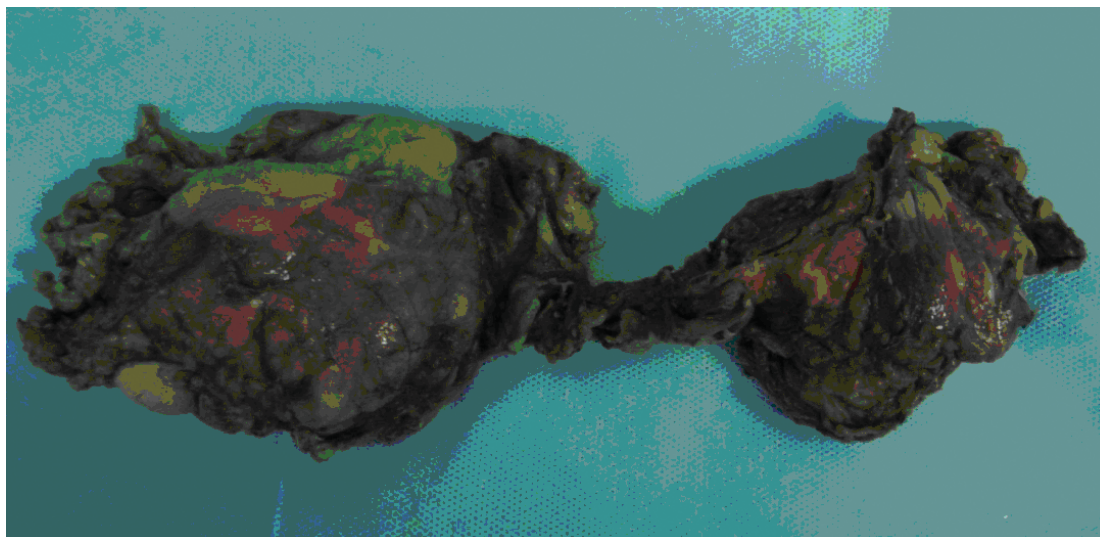
Case 3: Patient N., male 43 years, got sick in the prison, received standard tetrad. With complicated urotuberculosis was admitted in Urogenital Clinic of Novosibirsk Research TB Institute. Diagnosis was: polycavernous tuberculosis of right kidney, afunctional right kidney, tuberculosis of the ureter and bladder, microcystis, MBT-. Spiral computer

tomogram (posterior view and anterior view) and radioisotope scintigram are showed on Fig. 3, 4 and 5. N. underwent nephroureterectomy followed by enterocystoplasty. Tuberculous kidney, ureter and bladder, removed as one block multiple renal caverns, fibrous microcystis, - are presented on Fig. 6. Cystogram before operation is demonstrated on Fig. 7, and after operation – on fig. 8.

## Discussion

Severe epidemic situation on TB in Siberia results in high incidence of UGT with every year more than 200 patients getting sick with this disease, from new-born till 65 and older. It is necessary to improve the education of doctors together with the population concerning UGT, because UGT has atypical manifestation. In Spain UGT was the most frequent form of extrapulmonary tuberculosis, accounting for 40.9% all TB cases between 1978 and 1989 years (11). In Europe, the lymphonodal TB is widely prevalent (12).

In the current study, UGT was observed predominantly in females (as male to female ratio of 1:1.5). However, there is contrary opinion in the literature; the male to female ratio is up to 3:1 (3, 11, 13-14). We think, UGT, as any other kidney disease, should be more often in female patients, because menses,



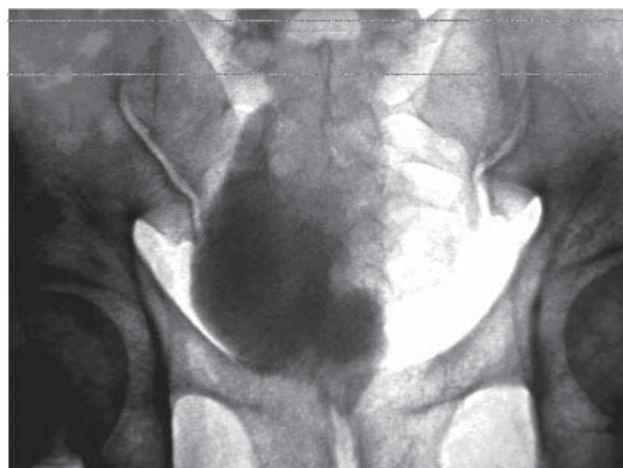
**Figure 6.** Tuberculous kidney, ureter and bladder removed as one block.



**Figure 7.** Cystogram before enterocystoplasty (V=20 ml)

pregnancy and inflammation of genitals may hinder the urine passage. Urinary stasis makes the possibility for fixation MBT to urothelium, and so, for developing renal TB.

UGT is a form of secondary TB, with vague symptoms and presentations, and is rare in children (15). In our study, UGT was also rare in children; we



**Figure 8.** Cystogram after enterocystoplasty (V=680 ml), incontinence is absent

observed only 13 out of 208 cases with UGT aged below 14 years.

To be considered UGT the disease should be in the lower genitourinary tract rather than the kidney. TB of the lower genitourinary tract most commonly affects the epididymis and the testis, followed by bladder, ureter, prostate, and penis (16). Nevertheless, our findings were contrary and we have found more often renal TB rather genital TB (9-10, 12).

Bladder tuberculosis is always secondary to renal TB, however quite often renal TB may start with voiding symptoms such as dysuria, frequent and painful urination (up to 80 times per day). Urinalysis reveals – pyuria, erythrocyturia and growth of unspecific bacteria is possible. Because TB is epidemic in Russia the National Russian Urological

**Table 1.** Results of combined therapy (modified “tetrad”+ trospium chloride) in patients of a second group with active tuberculous cystitis grade 3 (n=26)

	Before treatment	After 3 months	P
Frequency of day mictions	36.8 ±5.8	8.6 ±1.7	<0.05
Frequency of night mictions	8.7 ±1.3	1.9 ±1.9	<0.05
Bladder capacity	37.4 ±6.2	174.9 ±8.5	<0.05
Qmax (ml/sec.)	14.7±2.1	22.9±3.8	<0.05
Qave (ml/sec.)	8.4±2.5	16.0±3.3	<0.05
Intensity of pain (score)*	4.6 ±0.7	1.3 ±0.4	<0.05
Quality of life (score) *	1.5 ±0.2	4.3 ±0.2	<0.05

\*Intensity of pain and quality of life were estimated in score scale from 1 to 5 (1 – minimal, 5 – maximal)



Congress approved a resolution in 2007, that all cases of infections of the urogenital tract should be suspicious for TB, and first line therapy should exclude antibacterials affecting MBT (fluorquinolons, rifampicin, streptomycin or amycacin). All patients with an infection of the urogenital tract should be investigated for TB by culture and/or microscopy. Only after TB is excluded, they may be treated with fluorquinolons.

Standard chemotherapy for bladder TB demonstrates poor results: only 42.1% could be cured, 57.9% developed complications such as posttuberculous cystalgia (36.8%) and microcystitis (21.1%). In patients who received the combined treatment, outcome was favourable: urinary frequency reduced about 75%, bladder capacity increased an average of 4.7 fold. None of these patients developed true microcystitis. Thus the combination chemodrug plus trospium chloride is more effective and should be recommended to all patients with bladder TB grade 2-3.

The prevalence of incontinence as whole in different countries may be as high as 58.4% (17-19). Probably, the predominance in the pathogenesis of bladder TB fibrous processes allows the patients to avoid this complication. Incontinence in five men was due to total destruction of the prostate being outside sphincter of the bladder.

## Conclusions

Urogenital tuberculosis is not a rare disease in the region with high level of the incidence of TB. The diagnosis of UGT is difficult due to non-specific clinical features in addition to poor knowledge of this disease. Complicated forms of UGT, especially bladder TB, require additional pathogenetic therapy.

## Conflict of Interest

None declared.

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