Urogenital Tuberculosis as a Part of Extrapulmonary Tuberculosis: Epidemiology and Some Aspects of Diagnosis and Therapy

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1 Introduction

Tuberculosis (TB) is a current public health problem, remaining the most common worldwide cause of mortality from infectious disease. Tuberculosis (both pulmonary and extrapulmonary) leads to male and female infertility (Khanna & Agrawal, 2011; Kulshrestha et al., 2011; Wise & Marella, 2003; Tzvetkov & Tzvetkova, 2006; Lenk & Schroeder, 2001; Scherban et al., 2010; Wise & Shteynshlyuger, 2008), it is a sexually transmitted disease (Scherban & Kulchavenya, 2008) that explains why TB is not only a medical, but also a big social problem.

Urogenital tuberculosis (UGTB) is ancient but still now an unsolved problem. Clinical features are flexible and variable, UGTB mimics numerous other diseases that results in delayed diagnosis. Despite of about 7000 articles with key words “urogenital / genitourinary tuberculosis”, there is none good multicenter study with high level of evidence on this problem. UGTB is an embodiment of contradictions – from terms and classification till therapy and management. Nevertheless we have to overcome this quagmire for best understanding this eternal enigmatic and potentially fatal dangerous disease.

2 Terminology and Classification

There are no unique classifications of extrapulmonary tuberculosis (EPTB) or urogenital tuberculosis. Some authors consider EPTB as TB of any organ, excluding exactly broncho-pulmonary lesion, so pleural TB they relate to the one of the form of EPTB too. Others think that division of lung and its cover pleura on two separate organs is incorrect, and ascribe both organs to pulmonary tuberculosis (PTB) and instead of EPTB use a term Extrathoracal Tuberculosis (ETTB), or extrarespiratory tuberculosis, which merge TB of all organs out of thorax. This is a reason for confusion with proportion of EPTB/ETTB forms.

The first note of urogenital TB was made by Porter (1894). Later Wildbolz (1937) suggested the term genitourinary TB. The term “Urogenital TB” is more logical, because kidney TB, which is usually primary, is diagnosed more often than genital TB (Singh et al., 2013). Only 53% of patients with kidney TB had genital lesions, but in 61.9% patients with epididymorchitis and in 79.3% patients with TB of the prostate a renal lesion could be diagnosed (Kulchavenya, 2009; Gómez García et al., 2010). In UGTB, the kidneys are the most common sites of infection and are infected through hematogenous spread of the bacilli, which then spread through the renal and genital tract (Abbara & Davidson, 2011). Although some authors believe that tuberculosis often affects the lower genitourinary system rather than the kidney. They found that tuberculosis of the lower genitourinary tract most commonly affects the epididymis and the testis, followed by bladder, ureter, prostate, and penis (Wise & Shteynshlyuger, 2008).

Actually the term UGTB is incorrect too, because it includes kidney TB, male genital tuberculosis (MGTB) and sometimes even female genital tuberculosis (FGTB) – but all these forms of the disease have their own clinical features and require their own approaches to diagnosis and management. Although there is an opinion, that, as TB is an infection disease caused by M. tuberculosis (Mtb), it should be diagnosed by identification of the infection agent only and therapy should be directed on elimination of Mtb only – without separation on particular forms with individual approach to the diagnosis and treatment.
3 Epidemiology

In 1984 EPTB remained a major health problem in Australia, where 24.3% of all new TB notifications were extrapulmonary origin. The commonest sites of disease were the lymph nodes, urogenital tract, pleura and bone (Dwyer et al., 1987). By the 1980s, the availability of antituberculous chemotherapy reduced the incidence and prevalence of tuberculosis. Changing patterns of population emigration and the development of large pools of immune-compromised individuals reversed the downward trend of tuberculosis (Wise & Marella, 2003).

In past century in Oklahoma a greater proportion of newly diagnosed cases of extrapulmonary tuberculosis occurred in nonwhites. This was especially true to TB meningitis, TB lymphadenitis, and miliary tuberculosis (Snider, 1975). These days EPTB was frequent in Africa and had a great severity due to delayed diagnosis and multifocal forms (Aubry et al., 1979). At Boston city in 80-ies of last century EPTB represented 4.5% of all new cases of active tuberculosis and tended to occur in older patients. Sites of involvement included lymph nodes, genitourinary tract, bone and articular sites, the meninges, peritoneum, adrenal glands, pericardium, and miscellaneous sites, in this order (Alvarez & McCabe, 1984).

In Spain from 1991 to 2008 among the 2,161 cases diagnosed, 1,186 were PTB and 705 EPTB. The number of EPTB cases decreased more slowly than PTB. EPTB increased from 30.6% of cases in 1991-1996 to 37.6% in 2003-2008 (lymphatic site increased 27%) (Garcia-Rodriguez et al., 2011). Authors concluded, that whilst there has been a reduction in the overall incidence of TB, the proportion of EPTB increased that could be explained by an increase in life expectancy and the predominance of women in the population, and by a decline in BCG vaccinated patients (Garcia-Rodriguez et al., 2011). In Nepal common sites for EPTB were lymph nodes (42.6 %) and peritoneum and/or intestines (14.8%) (Sreeramareddy et al., 2008).

Within the last decade the spectrum of EPTB in Siberia has changed significantly (Kulchavenya, 2013). TB of the central nervous system almost doubled from 4.9% to 8.7%, mostly due to co-morbidity with HIV. Bone and joints TB increased by about half from 20.3% to 34.5%, and among this group TB spondylitis with neurological disorders predominated, the most debilitating form of the disease. The proportion of UG TB decreased from 42.9% to 31.7%. In contrary, there was a decrease of peripheral lymph nodes TB from 16.7% in 1999 to 11.2% in 2011, with fistulous disease still frequent. At the end of the last century ocular TB accounted for 7.4% and in 2008 (in 2009 listed in “others”) for 4.4% of the patients with EPTB. Accordingly, in 1999 other form of TB accounted for 7.8% and in 2009 for 15.8% (in 2011 – 13.9%). The increase is partly due to inclusion of patients with ocular TB in this group, and partly due to better diagnosis of TB of the skin, abdominal organs, breast etc (Kulchavenya, 2013).

EPTB had an increasing rate in Turkey in 2001-2007. The reason remains largely unknown (Gunal et al., 2011). The most commonly seen two types of EPTB were genitourinary TB (27.2%) and meningeal TB (19.4%). TB of bone/joints, pleura, lymph nodes, skin, and peritoneal TB occurred at a frequency ranging from 9.7% to 10.7% (Gunal et al., 2011). In 2009 almost one-fifth of United States TB cases were extrapulmonary; unexplained slower annual case count decreases have occurred in EPTB, compared with annual case count decreases in pulmonary tuberculosis (PTB) cases. From 1993 to 2006 among 253,299 cases, 73.6% were PTB and 18.7% were EPTB, including lymphatic (40.4%), pleural (19.8%), bone and/or joint (11.3%), genitourinary (6.5%), meningeal (5.4%), peritoneal (4.9%), and unclassified EPTB (11.8%) cases (Peto et al., 2009). In France in 2012 the most frequent clinical presentations of EPTB were lymphadenitis, pleuritis and osteoarticular TB. Peritoneal, urogenital or meningeal TB was
less frequent, and their diagnosis was often difficult due to the wide differential diagnosis and the low sensitivity of diagnostic tests including cultures and genetic amplification tests (Mazza-Stalder et al., 2012). In some countries the rate of growth of bone & joint TB reached the leading position among EPTB (Kulchavenya, 2013). Location of TB on the spine remains the most common form of skeletal TB, representing 62.2% of all osteo-articular locations (Didilescu, C. & Tănăsescu, M., 2012; Wiler et al., 2010). The skeletal form was responsible for 3% of the total number of cases, with 50% of these due to spinal tuberculosis (Vilar et al., 2006).

UGTB usually results from the reactivation of old, dormant tuberculous diseases by pathogens of the Mycobacterium tuberculosis complex (Lenk, 2011). It was the second most common form of EPTB in countries with severe epidemic situation and the third most common form in regions with low incidence of TB (Colbert et al., 2012; Kulchavenya et al., 2012; Lima et al., 2012), with more than 90% of cases occurring in developing countries (Abbara et al., 2011). EPTB comprises 20-25% total burden of the disease in which UGTB is 4% by opinion of Singh et al., 2013. It has been well described that the urogenital system is a common site of EPTB in adults, but the true incidence of UGTB is less clear, and reports have varied from 4% to 73% (Zarrabi & Heyns, 2009). It was found that UGTB represented 27% of extrapulmonary cases. Renal involvement in TB can be part of a disseminated infection or a localized genitourinary disease. Renal involvement by TB infection is underdiagnosed in most health care centers (Daher et al., 2013). In nowadays UGTB is not commonly encountered in general urological practice in Australia and New Zealand. However, this infection is easily overlooked unless clinicians maintain a strong awareness of its possibility (Patterson et al., 2012). In Japan because of the progress in anti-TB chemotherapy, it has become quite rare to diagnose patients with UGTB, however, the incidence of tuberculosis remains comparatively high, particularly in elder patients, among advanced countries (Miyake & Fujisawa).

Lin et al. (2009) in retrospective study compared patients with EPTB and PTB in southern Taiwan. They found, that among total of 766 TB patients in 102 (13.3%) EPTB was diagnosed, and in 664 (86.7%) – PTB, and 19.6% of EPTB patients also had PTB. The most frequently involved EPTB site was the bone and joints (24.5%). The incidence of EPTB vs. PTB decreased significantly for each decade increase in patient age. Multivariate logistic regression analysis showed that being female, not being diabetic, having end-stage renal disease and not smoking were independent risk factors for EPTB (Lin et al., 2009).

131 history cases of UGTB patients, who were revealed in 2009 – 2011 years in Siberia, were analyzed (Kulchavenya, 2013). The most common form was kidney tuberculosis (74.8%). Isolated kidney tuberculosis (KTB) more often has met in women – 56.8%. Patients of middle and old age more often were revealed in stage of cavernous KTB; young patients had small forms. Among all UGTB patients asymptomatic course was in 12.2%, among KTB - in 15.9%. Every third patient complained of flank pain and dysuria (accordingly 35.2% and 39.8%), 17% presented toxicity symptoms, 9.1% - renal colic, 7.9% - gross-hematuria. M.tuberculosis in urine was found in 31.8% in all levels of isolated KTB as whole. UGTB has no any specific symptom, even sterile pyuria meets only in 25% only. The acute onset of tuberculous orchiepidydymitis was in 35.7% of patients, hemospermia was in 7.1%, dysuria - in 35.7%. The most common complaints for prostate tuberculosis were perineal pain (31.6%), dysuria (also 31.6%), and hemospermia (26.3%). Mtb in prostate secretion / ejaculate was revealed in this group in 10.5%. Authors concluded that all urogenital tract infections should be suspected on UGTB in patients living in the region with high incidence rate, who had contact with tuberculosis infection, who has recurrent course of the disease, resistant to standard therapy.
Isolated epididymo-orchitis is an unusual presentation of tuberculosis (Shenoy et al., 2012). In study of Singh et al. (2013), in UGTB kidney was the most affected organ (64.9%) following ureter (27.35%), urinary bladder (17.09%), prostate (3.4%) and epididymis (5.19%). In this study, none case of testicular and penile tuberculosis was encountered. Tuberculous epididymo-orchitis should be considered in the patients who present with a scrotal mass. The preoperative differentiation of tuberculous epididymoorchitis from non-tuberculous epididymo-orchitis and testicular tumor is difficult. In patients who have epididymal and testicular lesions, surgical excision provides the diagnosis (Suankwan et al., 2012). In Spain of the 371 male TB patients 34 (9.2%) had orchiepididymitis. Mean age was 52.7 years and the presenting symptom was scrotal swelling and/or pain. Over 50% of cases involved the right testis. MGTB associated renal tuberculosis and active disease in extraurological organs presented in 64% and 19.2% of cases, respectively. Diagnosis was established by culture of Mycobacterium tuberculosis recovery from urine and/or purulent scrotal exudates (Gómez García et al., 2010).

Some authors have found that UGTB affects more men than women (Benchekroun et al., 1998; Figueiredo & Lucon, 2008; el Khader et al., 2001, Tanthanuch et al., 2010; Nurkić M., 2006); others – exactly the contrary (Aubry et al., 1979; García-Rodríguez et al., 2011; Mazza-Stalder et al., 2012; Singh et al., 2011; Singh et al., 2013). It have been seem UGTB, as any other kidney disease, should be more often in female patients, because menses, gravidity, inflammation of genitals may hinder the urine passage. Urinary stasis makes the possibility for fixation Mtbe to urothelium, and, so, for developing renal TB.

As whole a proportion male:female among EPTB patients depends on form of the disease. Concerning UGTB superiority of female patients is when UGTB includes both urological and gynecological TB, but in some regions there were female superiority among urological TB too. Actually, for better estimation of epidemic situation UGTB should me divided on urological TB (including male genital TB), and female genital TB.

In eastern Sudan of the 2778 women presenting with various gynecologic symptoms, 44 suspected cases of FGTB were identified. Granulomatous tissue reactions were observed in 25 of the suspected FGTB cases, yielding an incidence of 0.9%. The majority (80%) of these patients presented with chronic pelvic and lower abdominal pain; however, 68.0% presented with pelvic mass, cyst and/or abscess; 48.0% had dyspareunia; 40.0% were infertile; 28% had menstrual dysfunction; 20.0% had dysmenorrhea; and 4.0% experienced postmenopausal bleeding. Body mass index, residence, and educational level were significantly different between women diagnosed with FGTB and those where FGTB was excluded (P values=0.02, 0.03, and 0.01, respectively). However, no significant differences were found in age and Bacillus Calmette-Guérin vaccination status (Ali & Abdallah, 2012).

Over a period of 30 months (July 1986 - December 1988) 57 cases of genital tuberculosis were diagnosed at Tygerberg Hospital (Margolis et al., 1998). Forty of these cases were diagnosed as a result of routine screening in 650 patients who presented with infertility and the other 17 were diagnosed in patients admitted to the gynaecological wards. The prevalence in patients presenting with infertility was 6.15%. The commonest gynaecological presenting symptom was infertility (73.7%). Dysmenorrhea in 29.8% and deep dyspareunia in 12.3% were the only other frequently occurring gynaecological symptoms. Menstruation was normal in 50 patients (87.7%) (Margolis et al., 1998). In another study FGTB patients presented with infertility (70%), pelvic/abdominal pain (55%), and menstrual disturbances (25%). Tuberculosis involved the endometrium in 55.88%, tubes in 23.53%, ovaries in 14.71% and cervix in 5.88% of the 68 cases (Mondal & Dutta, 2009). In fifteen-year retrospective study of 110 cases in eastern India a total number of 110 cases of FGTB from 92 patients were included. Patients presented
with infertility (70%), pelvic/abdominal pain (55%) and menstrual disturbances (25%). Female genital tuberculosis involved the vulva (2), vagina (1), cervix (5), endometrium (66), fallopian tube (24) and in 12 patients - ovaries (Mondal, 2013).

A total of 85 women of genital TB, who underwent diagnostic laparoscopy for infertility or chronic pelvic pain were enrolled in the retrospective study in India. Most women were from poor socioeconomic status (68.1%). Past history of TB was seen in 34.1% women with PTB in 22.35% women with EPTB. Most women presented with infertility (90.6%; primary 72.9%; secondary 17.6%) while the rest had chronic pelvic pain (9.4%). Diagnosis of genital TB was made by histopathological evidence of TB granuloma in 18.8%, positive polymerase chain reaction (PCR) in 64.7% and laparoscopic findings of genital TB in 47.1%. The various findings on laparoscopy were tubercles on peritoneum (12.9%) or ovary (1.2%), tubovarian masses (7.1%), caseous nodules (5.8%), encysted ascitis in 7.1% women. Various grades of pelvic adhesions were seen in 65.8% women (Sharma et al., 2008).

A retrospective clinicopathological study of 1,548 cases of FGTB between 1940 and 2011 was conducted in Turkey. The mean age of the cases was 29.49 years. Involvement of the endometrium was noted in 1,073, fallopian tubes in 164, cervix in 157, and 154 had multiple organ involvement. Clinically, 115 cases (7.4%) were diagnosed as having primary infertility and 12 cases (0.8%) as having secondary infertility. There was a coexistent carcinoma in 1.5% of the cases. Peritoneal tuberculosis in 21 cases and tuberculous lymphadenitis in 7 cases were seen as well (Türkmen et al., 2012).

## 4 Predisposition

About 2 billion people are infected with Mycobacterium tuberculosis; they are carriers of latent infection, forming a large reservoir for reactivation of tuberculosis (Barry et al., 2009). Thus any contemporary person has a risk to be infected with Mycobacterium tuberculosis (Mtbb) and, in unfavorable conditions, to get sick with TB. Nevertheless, the infection of human organism with Mtbb doesn’t lead to disease obligatory, by all means. Recent studies have revealed numerous polymorphisms implicated in host susceptibility to TB. Human organism may have an innate resistance to Mtbb. Object lesson of this fact was “Lubeck disaster”. Between 10 December 1929 and 30 April 1930, 251 infants born in the old Hanseatic town of Lubeck received three doses of BCG vaccine by the mouth during the first ten days of life. Of these 251, 72 died of TB, most of them in two to five months and all but one before the end of the first year. In addition, 135 suffered from clinical TB but eventually recovered; and 44 became tuberculin-positive but remained well. The vaccine used was later found to have been contaminated with a human tuberculosis strain being studied in same lab (Wilson G., 1931). All children were equally infected by Mtbb – and some of them died, some of them – got sick with clinical TB, and 17.5% remained healthy, because they had good innate resistance to TB.

Factors leading to the increased incidence of tuberculosis include the high incidence of tuberculosis among the AIDS population, and the emergence of drug-resistant strains of tuberculosis (Gusmão et al., 1998; Fekak et al., 2003) TB with AIDS tends to occur in a younger population, is often extrapulmonary or with atypical lung involvement. Drug resistance is similar in patients with and without AIDS (Cremades Romero et al., 1998).

A cross-sectional study on extra pulmonary tuberculosis suspected patients was conducted at University of Gondar Hospital from January 2012 to April, 2012. The overall prevalence of smear positive EPTB was 34 (9.9%), and half of them (52.9%) were positive for human immunodeficiency
virus. Of these cases of EPTB, lymph node tuberculosis constituted the largest proportion (82.4%). Previous history of tuberculosis (OR = 4.77, 95% CI 1.86-12.24), contact to a known tuberculosis cases (OR = 6.67 95% CI 2.78-16.90), history of underlying diseases (OR = 2.79 95% CI 1.15-6.78) and income (OR = 12.9 95% CI 2.25-68.02) were significantly associated with extra pulmonary tuberculosis infection (Zenebe et al., 2013).

For UGTB poor prognostic factors included age over 65 years (HR = 4.03; 95%; CI: 1.27-12.76), cardiovascular disease (HR = 5.96; 95% CI: 1.98-17.92), receiving steroids (HR = 10.16; 95% CI: 2.27-45.47), not being treated (HR 4.81; 95% CI 1.12-20.67) (Hsu et al., 2011).

Furthermore, infectious adverse events associated with intravesical instillation therapy with bacille Calmette-Guérin (BCG), which is one of the most useful agents against non-muscle invasive bladder cancer, are frequently developed (Wise & Marella, 2003; Drechsler & Kirch, 2010; Miyake & Fujisawa, 2011; Kulchavenya et al., 2012). Congenital anomalies of urogenital tract, renal cysts, kidney transplantation and urolithiasis significantly increase a risk of development UGTB. The incidence of tuberculosis has been estimated to be as much as 10-fold higher among renal failure patients than among the general population (Chan et al., 1996; Gusmão et al., 1998; Kulchavenya & Muzyko, 2007; Korzeniewska A et al., 2009; Rabbani et al., 2011; Takeshita et al., 2012).

5 Pathogenesis of TB infection

Most common route of transmissions of Mtb is respiratory one, when infectious can be spread by coughing, sneezing, laughing, singing, or just talking. Also alimentary transmission is possible – usually through milk from ill cows; direct and indirect physical contact, including sexual; iatrogenic transmission with BCG instillation for bladder cancer therapy; transplacental transmission (unusual); blood transmission through a mosquito bite - extremely rarely (Kulchavenya, 2009).

Independent of the route of infection Mtb are spread by bloodstream and lymphatic system throughout the body (so-called primary dissemination). Of course, direct contact more often leads to the skin TB, alimentary route – to intestinal TB, prostate TB may be a cause of a genital TB in sexual partner etc. But after respiratory contamination lungs may by intact, and kidney or lymphonodal TB develops, as well as TB meningitis after alimentary contamination is possible (Brühl & Walpert, 1989; Türkmen et al., 2012). Very rare case of TB of placenta is shown below.

Case: Women 24 year, married, was examined in time of pregnancy by standard volume, was estimated as healthy. She had never any contact with TB infection. Delivery was in time, normal, physiological with healthy girl (weight 3200 g, length 51 sm). As in Russian Federation in big clinics placenta is investigated by histology normally in any case, placenta of our patient was investigated too. Pathohistology revealed TB inflammation with cells of Pirogov-Langhans, and Mtb in the specimen, colored by Ziehl-Neelsen technique. Figures 1-2 demonstrate TB of placenta. In 3 month ultrasound investigation shown a calcified focus in the right ovarium. Baby remained well.
Figure 1: A large epithelioid-cell granuloma with caseous necrosis in the center (is shown by arrow). x100. Hematoxylin and eosin.

Figure 2: TB caseous necrosis masses (is shown by arrow). x100. Hematoxylin and eosin.
6 Classification

For real estimation of epidemic level the disease should be in-time diagnosed and well classified. UGBT is an infectious disease of kidneys, urinary tract and male genitals, caused by M. tuberculosis. Clear definition and classification are necessary for correct therapy. Classification of any disease includes dispersion on forms and stages and exact definition for each stage. Each stage implies different approach to the management, so accurate classification is a base for good results of the therapy.

We proposed a following classification (Kulchavenya, 2004) of UGTB:

I. Kidney TB (KTB);
II. Male genital tuberculosis (MGTB);
III. Female genital tuberculosis (FGTB);
IV. Generalized UGTB when both kidneys and genitals are involved.

6.1 Kidney TB is divided on:

1 stage – non-destructive form, TB of parenchyma.

Tuberculosis of the renal parenchyma – minimal initial form of nondestructive nephrotuberculosis, when it is possible not only clinical, but also anatomic recovery. Urinalysis in children may be normal, although in adults may be found moderate leucocyturia. Radiographic signs of renal disease are absent. The structure of pelviocalyceal system is normal, destruction or retention are not assigned.

2 stage – small-destructive form, TB papillitis.

Tubercular papillitis may be one-and two-sided, single and multiple. M. tuberculosis in urine is not found always; usually is complicated by urinary tract tuberculosis. Should be cured by chemotherapy; with in-
adequate etiopathogenetic therapy ureteral strictures may form that require surgical correction. The prognosis is favorable.

3 stage – destructive form with one or two caverns (cavernous kidney TB).

Cavernous renal tuberculosis pathogenically develops by two ways - from tuberculosis of parenchyma or from papillitis. In the first case a subcortical cavity is forming, not associated with the CPS, the clinical picture is similar to renal carbuncle. Mostly such cavern is diagnosed after surgery. Cavernous nephrotuberculosis can be mono- and bilateral. If in one kidney tubercular papillitis is diagnosed, and in another - a cavern revealed, the case is classified as cavernous nephrotuberculosis, by more severe form of disease. The complications develop in more than a half of the patients. Usually cavernous nephrotuberculosis requires surgery (partial nephrectomy, plastic of ureter)

4 stage – widespread destructive form with more than 2 caverns (policavernous kidney TB).

Polycavernous renal tuberculosis presupposes occurrence of several cavities, which may lead to decreasing of renal function. As an extreme case, pyonephrosis may develop with the formation of the fistula. At the same time the self-recovery is possible, the so-called «kidney’s autoamputation» - imbibition of caverns with calcium salts and complete obliteration of the ureter. Complications develop almost always, the contralateral kidney is often involved too. Usually is cured by radical operation.

5 stage – urinary tract tuberculosis (UTB) – secondary for KTB, includes TB of ureter, bladder TB of 1-4 grades, urethral TB. Bladder TB is divided on following grades:

- 1 stage – Infiltrative form - tubercles;
- 2 stage – Ulcerous form – erosive;
- 3 stage – spastic cystitis (false microcystis) actually overactive bladders;
- 4 stage - true microcystis, up to full shrinkage of the bladder.

Complications of KTB/UTB: strictures, fistula, renal failure, arterial hypertension.

6.2 Male Genital Tuberculosis (MGTB) is divided on:

- Orchiepidydimitis (mono- and bilateral)
- Prostate TB (infiltrative or cavernous forms)
- TB of seminal vesicles
- TB of penis

Complications of MGTB: strictures, fistula, infertility, sexual dysfunction.

Clinical features and symptoms significantly varied between different forms of UGTB. The approach to the therapy and management of UGTB should be differential. KTB 1-2 levels should be treated with chemotherapy, KTB 3 level may require partial nephrectomy, KTB 4 level is indicated for nephrectomy – by open surgery or laparoscopically. Stricture of ureter is indicated for reconstructive surgery only in KTB 1-3 levels, KTB 4 level with stricture of ureter is indicated for nephrureterectomy. Bladder TB 1-2 grades should be treated by chemotherapy, bladder TB 3 grade requires additional prescription of trospium chloride, bladder TB grade 4 is indicated for cystectomy and reconstructive enteroplastic operation.
MGTB should be treated with chemotherapy; fistula, discharge sinus are indicated for surgery. Generalized UGTB is managed depending on forms of KTB and MGTB.

Chemotherapy for any form of UGTB includes initial intensive phase and continuation phase, which should be different accordingly clinical classification as well as drug sensibility of M. tuberculosis. For un-complicated KTB 1 level 6-month’s standard chemotherapy with 4 anti-TB drugs (isoniazide (H), rifampicin (R), pyrazinamide (Z), streptomycin (S)) may be enough; KTB 2 level requires 8 months of the therapy, KTB 3-4 levels – more then 8, and S should me excluding from the scheme, but fluoroquinolones and PAS, cycloserin should be added as well as pathogenetic therapy.

Thus, UGTB is multivariant disease, and standard unified approach to it is impossible. Join term “UGTB” has insufficient information in order to estimate therapy, surgery and prognosis – as well as to evaluate the epidemiology. Uniform approach to the therapy and management of UGTB independently of clinical forms leads to poorer results, then individual one. Using clinical classification will improve the efficiency of the therapy of UGTB. Diagnosis “UGTB” as whole has a little information, it is insufficiently both for estimation of epidemiology and choosing of approach of the therapy. The clinical classification is simple and clear, it is enough for estimation of the form and stage of disease and for definition of correct optimal treatment.

7 Clinical Features

UGTB usually results from the reactivation of old, dormant tuberculous diseases by pathogens of the Mycobacterium tuberculosis complex. The diagnosis of tuberculosis of the urinary tract is based on the case history, the finding of pyuria in the absence of infection as judged by culture on routine media and by radiological imaging (Lenk, 2011). In the study of el Khader et al. (2001) the most frequent clinical symptoms were irritative symptoms (47.3%). Fever, anorexia and weight loss were rare (11%). 16% of patients had an isolated genital lesion. 14% presented with renal failure (mean serum creatinine: 18 mg/l). Only 5.2% presented with bacilluria. Urography showed abnormalities in 80% of cases. The most frequent abnormality was a non-functioning silent kidney in 40.3%. The clinical presentations of tuberculous epididymo-orchitis included scrotal mass (80%), scrotal pain (44%), micturition syndrome (8%), urethral discharge (4%), and scrotal fistula (4%). One third of the patients had pulmonary tuberculosis.

Sixteen percents of the patients had underlying human immunodeficiency virus infection (Suankwan et al., 2012). Benchekroun et al. (1998) analyzed 80 patients with UGTB between 1985 and 1995. These patients consisted of 50 males (62.5%) and 30 females (37.5%) with a mean age of 38 years (range: 20 to 50 years). Intravenous urography revealed silent kidney in 26% of cases, ureterohydronephrosis in 36% of cases, small bladder in 17% of cases, and was normal in only 5% of cases. Renal function was impaired in 32% of patients. The diagnosis was confirmed by a positive smear in the urine in 64% of cases, bladder biopsy in 20% of cases and pathological examination of the operative specimen in 20% of cases.

Urogenital tuberculosis raises major diagnostic problems due to the frequently atypical and misleading clinical features. It is a serious disease as the lesions are often multifocal and extensive, requiring major surgical resection and urinary tract reconstruction (Benchekroun et al.,1998). Diagnosis is often difficult because TB has a variety of clinical findings. It can mimic numerous other disease entities. A high level of clinical suspicion allows early diagnosis and timely initiation of proper management (Teo & Wee, 2011; Muttarak et al., 2005). The nonspecific clinical features of UGTB make the early and accurate diagnosis of the disease difficult. Hematuria, lower urinary tract symptoms, flank pain, and scrotal
swelling are the most common presenting features. Chronic epididymitis associated with a draining scrotal sinus is often associated with UGTB (Zarrabi & Heyns, 2009). The most presenting symptoms were polyuria, dysuria and acidic urinary pH with pyuria. 80% of the patients had abnormal imaging studies of the urinary system, with hydrenephrosis being the most frequently found condition (Tanthanuch et al., 2010). In review of 8961 cases from the world literature there was shown great difference between clinical features of UGTB in different regions depending on epidemic situation, advancing of country etc (Figueiredo & Lucon, 2008).

Patients usually exhibit local symptoms. Fever, weight loss and anorexia are uncommon. Eighty-nine percent of the patients had abnormal urinalysis: hematuria and/or pyuria (Kao et al., 1996). Patients can present with unusual complaints not immediately suspicious for tuberculosis (Colbert et al., 2012); this infection is easily overlooked unless clinicians maintain a strong awareness of its possibility (Patterson et al., 2012). In Moscow UGTB manifested with chronic cystitis in 13.1%, subacute orchepidydimitis in 13.1%, anatomofunctional alterations of the kidneys (hydronephrotic transformation, non-functioning kidney, ureteritis, etc.) in 28.5% of patients (Batyrov et al., 2004). The diagnosis of renal TB can be hypothesized in a non-specific bacterial cystitis associated with a therapeutic failure or a urinalysis with a persistent leukocyturia in the absence of bacteriuria (Lima et al., 2012). Non-optimal empiric therapy for urogenital tract infections (UTI) resulted in high level of co-morbidity UGTB and UTI, and old symptom “sterile pyuria” now lost its significance (Kulchavenya, 2010).

8 Laboratory Diagnosis

A delay in diagnosing UGTB is common and results in significant morbidity. Patients who are diagnosed at a late stage often have complications such as ureteral stricture with hydrenephrosis, a shrunken bladder, autonephrectomy, or destruction of the testis by a cold abscess. This is unfortunate, because effective medical therapy is readily available (Zarrabi & Heyns, 2009).

Diagnostic of UGTB stays on 4 columns: bacteriology, pathohistology, radiology and provocative test with therapy ex juvantibus, but some simple and cheap tests may be useful too.

8.1 Urinalysis in the Diagnostic of UGTB

Urinalysis is the least invasive method of diagnosing UGTB. The classically described “sterile pyuria” is not very sensitive or specific for UGTB, but persisting sterile pyuria in an individual at risk should increase the clinician’s index of suspicion (Zarrabi & Heyns, 2009).

The introduction of the 4-glass test according to Meares and Stamey (1968) was a great step forward to diagnose chronic prostatitis not only by symptoms, but also by investigation of segmented urine and prostatic secretion specimens to localize the inflammation/infecion to the urethra, bladder or prostate (or any of these combinations). Thus, for many generations the Meares and Stamey 4-glass test was considered as “gold standard” and recommended not only for research but also for the general practicing urologist as routine test for diagnosing chronic prostatitis (Nickel, 2003). Unfortunately, one had to realize that these recommendations were not followed by several reasons, because the test is i) time consuming; ii) difficult to perform; iii) costly; and iv) bothersome for the patient (McNauhghton-Collins et al., 2000).

This was mainly the reason why the pre-massage and post-massage 2-glass test (PPMT) was developed to facilitate the M&S 4-glass test (Nickel & Weidner, 2000; Nickel et al., 2006). However, by
the PPMT 2-glass test only the laboratory burden (cost) is reduced by reducing the number of specimens, but the discomfort for the patient remains the same, because the patient has to produce a midstream urine, interrupt micturition not to empty the bladder completely, because after the following prostatic massage by digital rectal examination (DRE) he is supposed to produce another urine specimen again during the same visit. First, not every patient can interrupt micturition before the bladder becomes empty. Second, voluntary stop of micturition converts laminar flow of urine in a turbulent one and thus provokes reflux of urine into the prostatic ducts, which is fraught with the risk to develop chemical burns, inflammation and prostatolithiasis. Another aspect using the M&S 4-glass test is probably even more serious. Patients assigned to the M&S 4-glass test are usually not informed that between VB1 and VB2 and thereafter continuous urination without interruption is necessary to produce a true midstream urine specimen which is necessary to i) diagnose concomitant cystitis and ii) serve also as basic comparative parameter by which localization of inflammation/infection to the urethra or prostate can be made possible. Interruption of urine flow between VB1 and VB2 and at the end of VB2 will lead to contraction of the prostate and thus contamination of urine with prostatic secretion.

We (Kulchavenya et al, 2011, 2012) developed a 3-glass test for screening of patients with clinical signs and symptoms of chronic prostatitis with the option of further tests for final diagnosis only in those patients where additional investigations are needed. This KE 3-glass test comprises three urine samples taken from only one continuous urine stream: VB1 comprises the first 10 ml, VB2 the midstream portion of a non interrupted stream, and VB3 the final portion at the very last end of the stream. As the prostate is a part of the external sphincter of the bladder, it contracts at the end of a micturition. Therefore the urine sample at the end of the micturition (VB3) corresponds practically to the urine sample after prostatic massage. However, the discomfort of prostatic massage by DRE can be avoided. Leucocyturia in the first portion (VB1) indicates an inflammation in the urethra, in the second portion (VB2) a general inflammation in the urinary bladder and/or upper urinary tract, and in the third portion (VB3) an inflammation in the prostate. Leucocyturia in all three portions may mirror inflammation of the total urinary system.

Therefore 3-glass test (i) allowed avoiding DRE for diagnosis of chronic prostatitis, and (ii) total leucocyturia is highly suspected on UGTB. Non-specific bacterial prostatitis as well as non-specific epididymitis very rare is accompanied by pyelonephritis. On contrary, MGTB combines with kidney TB in up to 80%. So patient with epididymitis and/or prostatitis, having pyuria in all 3 portions of urine is high suspicious on UGTB – if it is real pyuria, not contamination of urine by prostatic secretion, as inevitably in 4-glass test. In our study UGTB was revealed in patients with chronic prostatitis by 3-glass test in 1.8% (Kulchavenya et al, 2011).

8.2 Bacteriology

At least six specimens of urine, expressed prostatic secretion and ejaculate should be cultured, each onto at least three slants (Lowenstein - Jensen, Finn – II, Middlebrook 7H9-12) (Lenk, 2011). Nevertheless standard technique is positive in 36-57% of UGTB patients only (Kulchavenya, 2009; Batyrov et al., 2004; Joo Yong Lee et al., 2011; Tanthanuch et al.,2010). Positive cultures were by 15% higher, if sowing performed three times in one day (Zhuravlev et al., 2012). 22,654 samples of urine were investigated by method of concentration and homogenization by Petroff and inoculated on Loewenstein culture media. All urine samples were taken from 4,192 patients. Positive culture was found in 358 urine samples (1.58%), in 173 patients (4.13%) (Nurkić M., 2006). For MGTB diagnosis investigation in one day prostatic secretion, than post-massage urine, then ejaculate and post-ejaculate urine – by microscopy, culture and real-time polymerase chain reaction (PCR) each probe is recommended. Very important thing is the
shortest time between collection of urine, prostatic secretion, and ejaculate and its sowing; optimal time should not be more than 40 min. (Kulchavenya, 2010). In order to identify mycobacteria and to perform antituberculous susceptibility tests, direct preparations stained with Ziehl – Nielsen (ZN) method to evaluate a smear microscopically or PCR method are insufficient; cultivation of mycobacteria is necessary (Aslan et al., 2007). PCR was found to be useful in diagnosing early disease as well as confirming diagnosis in clinically suspected cases. False negative PCR was an important limitation in this technique (Thangappah et al., 2011).

TB is an anthropozoonotic disease; it is a reason for possible cross-contamination human-animal and opposite (Dumonceaux et al., 2011). Presence of Mycobacterium bovis in urine accounted for 4.2% - 12.5% of all UGTB cases (Blagodarnyi et al., 1990; Berta et al., 2011; Singh et al., 2011).

To overcome the limitations of current urine-based diagnostic assays of UGTB, isothermal microcalorimetry was used to detect the metabolic activity of Mtb and other commonly neglected pathogenic mycobacteria in urine and accurately determine their growth parameters (Kumar et al., 2012).

8.3 Pathohistology

One more problem of diagnosis of UGTB is loss of pathomorphological signs of TB, especially in co-morbidity with HIV-infection. For identification of Mtb biopsies and operation tissue should be investigated also by ZN method. Seventy eight tissue specimens (renal, prostate, epididymis, penile and soft tissue) from patients with clinically suspected UGTB were processed for both PCR and histopathological examination (HPE). In 87.1% samples, results for both PCR and HPE were coinciding. False positivity and false negativity was observed in 5.1% and 7.6% samples, respectively. With HPE as the gold standard, PCR has shown sensitivity of 87.5% and specificity of 86.7% and positive agreement between two tests was observed as significant. PCR results were obtained within a mean period of 3.4 days while those of HPE were obtained in 7.2 days. Authors concluded that tissue PCR is a sensitive and specific method for obtaining early and timely diagnosis of UGTB. Application of tissue PCR can augment the diagnostic accuracy in pathologically labelled granulomatous inflammations (Chawla et al., 2012). In another study the possibility of the early rapid diagnosis of renal tuberculosis by PCR of renal biopsy specimens was estimated. It was found, that the sensitivity and specificity of real-time PCR were respectively 93.3% and 56.7%. The sensitivity and specificity of the urine M. tuberculosis culture were respectively 23.3% and 100% (Sun et al., 2010).

There was no correlation between the histological findings and the mycobacteriological investigations. The investigation of tissue specimens on the presence of mycobacteria also from other organs of the urogenital tract is suitable method of the bacteriological proof of tuberculosis, especially in the absence or positive bacteriological findings from the urine or accessory gland secretion for the estimation of species and resistance of these bacteria (Lenk et al., 1986).

It is necessary to keep in mind that biopsy for confirming UGTB by histology may have serious complications (Kulchavenya, 2010; Silva et al., 2011) till generalization of TB in un-treated patient. Miliiary TB was diagnosed in the patient resulting from the hematogenous spread following TRUS-guided prostate biopsy (Chul, 2011). Although sometimes biopsy may be useful in diagnostic UGTB (Shenoy et al., 2012), and histologic follow-up was estimated as a good method for monitoring the efficacy of treatment. Transrectal prostate biopsy may be an important tool for the diagnosis and follow-up of prostatic tuberculosis (Lee et al., 2011).
8.4 Radiology

Radiology is good method for diagnosis of UGTB – both prostate and kidney TB. Unfortunately this method is useful only for late cavernous forms, but our aim is early diagnosis. Pyelograms disclosed abnormalities in 94% and most revealed late changes (Kao et al., 1996). Caverns of prostate and/or kidney are absolutely pathognomonic symptom, but caverns mean late-diagnosed complicated form, cavernous UGTB can’t be cured by chemotherapy (Kulchavenya, 2010).

8.5 Provocation Test

In many cases provocation test with injection of 20-50-100 units of tuberculin subcutaneously may be useful. All laboratory investigations including body temperature are repeated 24 and 48 hours after tuberculosis injection. The test is positive if leucocytosis, lymphocytopenia, leucocyturia, leucocytospermia and body temperature have increased by more than one degree. Also local reaction (hyperemia, induration in place of injection tuberculin) is to be taken into account. After provocative subcutaneous tuberculin test identification of MBT by culture or PCR increased by 16%. On the whole, this test improved the diagnosis of UGTB, especially the obscure, latent forms, to 63% (Kulchavenya & Kim, 2010).

8.6 Therapy ex Juvantibus

Therapy ex juvantibus may be 1st type, when patient receives antibiotic which doesn’t inhibit Mtb, and 2nd type, when patient receives antibiotics which inhibit only Mtb (Kulchavenya, 2009). For therapy ex juvantibus 1st type fosfomycin, cefalosporins, and nitrofurantoin are suitable. For therapy ex juvantibus 2nd type we can use isoniazide, PAS, protonamid, etionamid, ethambutol, pyrazinamide. For good results of the therapy ex juvantibus pathognomonic therapy also is indicated: phytotherapy with canefron, non-steroid anti-inflammatory drugs etc (Kulchavenya and Kim, 2010).

9 Therapy

Drugs that can cure most TB patients have been available since the 1950s, yet TB remains the world’s second most important cause of death by infectious diseases. Unfortunately, during about half a century none new drug was developed. In the same time resistance of Mtb has increased enormously. Mono-, poly, and multi-drug resistant Mtb to the basic antituberculous drugs was found in up to 52.2% of extrapulmonary TB patients and up to 78.7% in pulmonary TB patients (Kao et al., 1996). Antituberculous drug treatment is based on an initial 2 month intensive phase with three or four drugs daily followed by a 4 month continuation phase with only two drugs (Lenk, 2011).

Medical treatment of genital TB is somewhat different from that of other TB, because prostatotropic drugs have to be preferred. In countries with low incidence of TB three antituberculous drugs with bactericidal activity may be sufficient for bacterial eradication and prevention of resistance. In epidemic regions patients with MGTB should be treated with four or five antituberculous drugs: isoniazid 10 mg/kg + rifampicin 10 mg/kg + pyrazinamide 20 mg/kg + streptomycin 15 mg/kg + PAS 150 mg/kg (or ofloxacin 800 mg or levofloxacin 500 mg daily) simultaneously for two to four months, followed by six to eight months of chemotherapy with isoniazid and rifampicin only (Kulchavenya, 2010).

WHO recommended reducing the treatment time to nine or six months with 4 drugs (isoniazid, rifampicin, pyrazinamid and streptomycin or ethambutol); in complicated or combined cases the length of
the therapy may be 12-14 months. In cases of re-treatment, immunosuppression and HIV/AIDS the treatment time increases to nine or 12 months (World Health Organization, 2004; World Health Organization, 2008).

Chemotherapy for late-diagnosed complicated forms of UGTB is not enough effective, so surgery is indicated (Viswaroop et al., 2006). The organ-removing operations were conducted in 73% of patients (Batyrov et al., 2004). Surgery, whether in the acute setting (orchietomy, nephrostomy) or after medical treatment (nephrectomy, cystoplasty), still plays an important role in the treatment of patients with UGTB (Zarrabi & Heyns, 2009).

To improve the chemotherapy for complicated form of UGTB with bladder involvement modified scheme was developed (Kulchavenya, 2010). “Modified” tetrad included isoniazid 10 mg/kg + rifampicin 10 mg/kg + pyrazinamid 20 mg/kg + ofloxacin 800 mg during 2 months. This was followed by a 6-10 months treatment with isoniazid and rifampicin only. In addition from the first day of the therapy all patients received trosplum chloride 15 mg b.i.d during three months as pathogenetic treatment. The efficiency of modified tetrad was compared with results of the standard chemotherapy (isoniazid 10 mg/kg + rifampicin 10 mg/kg + pyrazinamid 20 mg/kg + streptomycin 15 mg/kg). The outcome analysis showed, that standard therapy was insufficient in more than a half of the cases: only 42.1% could be cured, 57.9% developed complications such as posttuberculous cystalgia (36.8%) and microcystis (21.1%). Patients treated by modified tetrad responded in a favourable manner: urinary frequency reduced about 75%, bladder capacity increased an average of 4.7 fold. Recovery was reached in 84.3%. Posttuberculous cystalgia developed in 15.7% only. None of the patients developed microcystis after the combined treatment. Tolerance to the treatment was good: only one patient had light side effect (mouth dryness).

10 Surgery

As UGTB is infection of the urogenital system, it should be cured by medicines, like any other UTI. And it may be cured – if it is diagnosed in-time, before development of destruction and caverns. Unfortunately, mostly due to late diagnostic, medical treatment may not result in resolution of symptoms. Surgical intervention and reconstruction of the urinary tract are frequently indicated (Viswaroop et al., 2006; Wise & Shteynshlyuger, 2008). The organ-removing operations were conducted in 73% of UGTB patients. Preoperative tuberculostatic therapy reduced frequency of postoperative complications. In early diagnosis, the organ was saved in operations in 9.4% only (Batyrov et al., 2004). It was found that such eradicative techniques as nephrectomy and nephretherectomy still prevail. Early drainage of the kidney for its decompression allows preservation of the kidney and following reconstructive surgery in 70.6% of cases. The number of early and later complications have considerably decreased (Zuban’ et al., 2008).

Bladder TB grade 4 (microcystis) is indicated for cystectomy following by enteroplasty (Kulchavenya and Krasnov, 2012; Kulchavenya et al., 2012). Urinary bladder rehabilitation either by augmentation cystoplasty or orthotopic neobladder reconstruction increases the bladder capacity and storage time and also preserves the upper tracts (Singh et al., 2010). Bladder and ureter reconstruction with ileum is a good option in difficult cases of lack or irreversible damage of the urinary way. Vesico-ureteral reconstruction letting urethral miction improves quality of life (Resina et al., 2009; Singh et al., 2010). Patients after full course of the therapy and, if it was indicated, surgery, should be under surveillance for 3-5 years with annual check-up and anti-relapse therapy, if necessary.
11 Conclusion

UGTB is enough often, but mostly overlooked disease. The main reasons for late diagnosis are lack of alertness on UGTB in urologists and general practitioners relative to patients with UTI, kidney anomalies, renal cysts etc; non-specific variable clinical features, decreasing positive cultures of Mtb due to non-optimal empiric therapy for UTI with prescribing of fluoroquinolones and amycacin. Standard chemotherapy is effective only for early diagnosed form of UGTB, in complicated form modified scheme with 5 anti-TB drugs in combination with pathogenetic therapy is indicated. Destructive forms of kidney and male genital TB can’t be cured by chemotherapy, the surgery is necessary.

EPTB cases include TB lymphadenitis, pleural TB, TB meningitis, osteoarticular TB, genitourinary TB, abdominal TB, cutaneous TB, ocular TB, TB pericarditis and breast TB, although any organ can be involved. Diagnosis of EPTB can be baffling, compelling a high index of suspicion owing to paucibacillary load in the biological specimens. A negative smear for acid-fast bacilli, lack of granulomas on histopathology and failure to culture Mycobacterium tuberculosis do not exclude the diagnosis of EPTB. Novel diagnostic modalities such as nucleic acid amplification (NAA) can be useful in varied forms of EPTB (Mehta et al., 2012).

References


