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The therapy for urogenital tuberculosis

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ABSTRACT

Tuberculosis (TB) is a communicable disease that is a major cause of ill health. Urogenital TB was a frequent urological disease in the pre-antibiotic era: about 20% of patients in urological hospitals had renal TB, mostly in the form of pyonephrosis.

We composed a narrative review of the literature with keywords "urogenital tuberculosis', "prostate tuberculosis" "kidney tuberculosis", "treatment of tuberculosis".

Urogenital TB (UGTB) includes TB of the kidney and the urinary tract and male and female genital TB. Each clinical presentation requires tailored antibiotic therapy depending on stage and general management. Anti-TB therapy should be multicomponent, continuous, long-lasting and controlled with a follow-up for 2-3 years. Otherwise, the risks of development of drug-resistance and relapse increase.

Index of suspicion on UGTB is generally low, causing a delay in diagnosis; consequently, complicated forms of UGTB respond poorly to anti-TB therapy, while timely diagnosed "minor" forms are curable medically without surgery. Even with timely diagnosed UGTB, non-optimal therapy may result in over-fibrosis, scarring and strictures of the urinary tract, making surgical repair inevitable. Nevertheless, we have a wide enough spectrum of anti-TB drugs to cure urogenital TB.

Keywords: Urogenital tuberculosis, Prostate tuberculosis, Kidney tuberculosis, Prostate tuberculosis, Treatment

1. INTRODUCTION

Tuberculosis (TB) is a contagious disease with high level of mortality. Even nowadays, with effective antibiotics available, TB is one of the top 10 causes of death throughout the world and the leading cause of death from a single infectious agent [1]. This statement was valid before the coronavirus disease 19 (COVID-19) pandemic which has started in March 2020. The World Health Organization (WHO) emphasized that COVID-19 pandemic reversed recent progress in reducing the global burden of TB disease [2]. The limited possibility of access to medical care resulted in delayed diagnosis and a large global drop in the number of people newly diagnosed with TB in 2020, compared with 2019 [3].

At a glance, decreasing incidence of TB is a positive tendency. However, in fact, the disease was diagnosed too late, when complications had already developed and resulted in an increased mortality rate. The consequence of the large drop in the number of newly diagnosed cases of TB in 2020 is an increase in the number of deaths from TB in this year. Globally, in 2020, there were an estimated 1.3 million deaths among human immunodeficiency virus (HIV)-negative people, and an additional 0.214 million deaths among HIV-positive people [3]. So, if mortality rate of TB was about 15% in 2019, it can be estimated that this rate was doubled in 2020.

Some believe that TB is a disease of poverty, while TB can affect anyone anywhere. Mostly (about 90%) TB affects adults. High incidence rate among children is a mirror of adverse epidemiological situation. Eighty seven percent of newly diagnosed TB patients lived in one of 30 high TB burden countries [1].

Tuberculosis is a disease caused by Mycobacterium complex: Mycobacterium tuberculosis (Mtb) or M. bovis. Lungs are exposed to TB (pulmonary TB, respiratory TB) in the majority

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of patients, but the disease can also affect any other organ (so-called extrapulmonary TB). Extrapulmonary tuberculosis (EPTB) includes any site other than lung parenchyma and can occur both in the presence and absence of active pulmonary TB or history of TB disease.

The spectrum of EPTB fluctuates from region to region, depending on many factors. Urogenital TB is the second-third most common site among all EPTB forms in some regions while it is rare and does not exceed 2-3% and in other regions. Which figure is real? In fact, many patients with urogenital TB remain undiagnosed, so they do not receive anti-TB therapy, that leads to the progress and dissemination of the disease. According to WHO reports only 38% of the patients with TB, caused by multi-resistant pathogen received appropriate therapy in 2019 [4].

Urogenital TB (UGTB) includes kidney and urinary tract TB and male and female genital TB. Co-morbidity with pulmonary TB may be found in 40 – 65% of cases – while isolated UGTB, solo lesion of urinary or genital system, is possible, too. Isolated UGTB is especially difficult to diagnose as it has no specific clinical features and hides under masks of other diseases, mostly urogenital tract infections, cancer and stone disease. In a series, 22% men had acute debut of male genital tuberculosis (MGTB) with no report of contact with TB infection or TB history [5]. Delayed diagnosis may result in surgery, while timely diagnosed disease (on early stages) may be cured by anti-TB drugs. Every second MGTB patient has also pulmonary or renal TB. As a rule, TB epididymitis (especially bilateral) and prostate TB are diagnosed together [5,6]. If there is no other evidence of Mtb, UGTB may be diagnosed based on positive tuberculin skin test, Interferon-Gamma Release Assay (IGRA)-test, QuantiFERON-test, histological picture of biopsy, by X-ray examination, when destructive cavities are revealed. Sterile pyuria is not evident now, as co-morbid UGTB and non-specific urogenital tract infections are diagnosed in 75% [5,7].

Georges Marion, (1869 – 1960), famous French surgeon and urologist had written: "Renal tuberculosis is extremely common. In the urology department every fifth bed patient suffers from renal tuberculosis and more than a third of all renal suppurations are of tuberculous origin. In 80% of cases of renal tuberculosis, the bladder is also affected. The disease progresses slowly, death is almost inevitable" [8].

2. METHODS

This article is structured as a narrative review of the literature with keywords "urogenital tuberculosis', "prostate tuberculosis" "kidney tuberculosis", "treatment of tuberculosis", "anti-TB drugs", "anti-TB therapy". Data were obtained from articles published in Russian and in English from journals indexed in PubMed, Google scholar, e-library. Articles mainly dedicated to anti-TB therapy for UGTB were selected and analyzed.

3. CLASSIFICATION

Urogenital TB is a combined term and covers renal TB, urinary tract TB, male and female genital tract TB [5,9]. Kidney TB is sub-classified into four stages depending on the level of destructive lesion [5,9]: TB of kidney parenchyma, TB papillitis with destruction of one or more calices, cavernous kidney TB with big destructive cavity of parenchyma and final incurable by the therapy stage is polycavernous kidney TB, terminal form with widespread destruction of parenchyma.

Chronic renal failure, flank fistula, arterial hypertension are complications of kidney TB as well as urinary tract TB.

Urinary tract TB is almost always or generally secondary to kidney TB; first appears as an edema and the next stages are infiltration, ulceration and fibrosis with development of a stricture of ureter (mostly in the lower third) or shrinked bladder, when surgery is indicated [8].

Tuberculosis of the urethra is a rare complication. It is usually diagnosed in the stage of a stricture.

Male genital tuberculosis is sub-divided into five categories [5, 9, 10]:

- Category 1: TB of the epididymitis (uni – or bilateral). TB epididymitis is a primary isolated form of UGTB in 21.5% of patients.
- Category 2: TB of the testis. This form of UGTB is always secondary to TB epididymitis. Every third patient has bilateral lesions, every tenth patient has a scrotal fistula. Sixty-two percent of patients with epididymo-orchitis has renal TB as well [10].
- Category 3: TB of the prostate. In 77% of men with any form of TB, prostate TB was found on autopsy, and mostly the disease was not diagnosed while these individuals were alive.
- Category 4: TB of the seminal vesicles. This form of UGTB is always secondary to prostate TB and leads to infertility. Usual outcome of TB of seminal vesicles is calcification [11].
- Category 5: TB of the penis. This form of UGTB is rare. TB of the penis is considered as a sexually transmitted disease [12-14]. TB of the penis may occur as a complication of Bacillus Calmette–Guérin (BCG)-therapy for bladder cancer [15,16].

Complications of MGTB are strictures, fistula, infertility and sexual dysfunction.

There is no unique therapeutic approach to all patients with any form of urogenital TB. Each localization of TB inflammation may require tailored antibacterial therapy as well as additional treatment; so detailed classification is useful for choosing the sort of the therapy.

As only male UGTB is within the scope of urological treatment, evaluation of female genital TB is not covered in this article.

4. THERAPY

Standard antibiotic regimens

Anti-TB therapy should be multi-component, continuous, long-lasting and controlled; after the end of the treatment the patient needs a follow-up for 2-3 years [17]. Otherwise, the risks of development of drug-resistance of the pathogen and relapse increase. WHO considers current anti-TB drugs highly effective and emphasizes that about 85% TB patients can be successfully treated with a 6-month drug regimen –provided that treatment is started timely, before severe complications occur [1]. If Mtb is suspected, standard oral four-component regimen of isoniazid, rifampicin, pyrazinamide and ethambutol may be effective in >90% for pulmonary TB patients [17].

Drug-resistant TB is nowadays a serious threat to global health security. Mtb can be resistant to one or more anti-TB drugs, but if it is resistant to even 3-5 drugs, while being sensitive to isoniazid and rifampicin, the pathogen is considered as mono – or multi-resistant. Strains with multidrug-resistance (MDR), that are defined as resistance at least to isoniazid and rifampicin, and extensively drug-resistance (XDR) that means Mtb are resistant to fluoroquinolones and second-line injectable drugs are very dangerous. WHO estimates that about half a million cases MDR – TB) are estimated to occur each year [2]. WHO recommended regimens of anti-TB therapy can only cure half of MDR-TB patients and 30% of patients with XDR-TB [18].

In general, the standard treatment regimen of UGTB is the same as for pulmonary TB, but there are some points, which should be taken into account. Streptomycin and kanamycin are not recommended for UGTB because of their nephrotoxic side-effect. Fluoroquinolones are widely used as anti-TB drug; mostly moxifloxacin, sparfloxacin, and levofloxacin. All these three fluoroquinolones demonstrate high efficiency in the treatment of patients with pulmonary TB. Nevertheless, levofloxacin should be preferred for the therapy of UGTB. Para-Aminosalicylic acid is indicated for the therapy of UGTB with involvement of pelvic organs and prostate TB. Amoxicillin/clavulanate is a popular antibiotic for urinary tract infections. Recent studies have shown that they are active on M. tuberculosis, too, especially if they are used with meropenem or imipenem together. Cycloserin affects both E. coli and M. tuberculosis, so this drug is indicated for comorbid UGTB and urinary tract infections. Patients with HIV co-infection who are treated by anti-retrovirus therapy should not receive rifampicin. Instead of this antibiotic rifabutin should be used for such patients. Rifampicin, as well as streptomycin is also contraindicated for patients after organ transplantation [19].

The most recent classification of the main anti-TB drugs is displayed in Table I.

Anti-TB drugs may be administered per os and parenterally, the dose is adjusted according to the weight of the patient (Table II).

Without treatment, two-thirds of TB patients will die, and the remaining one-third is likely to suffer from chronic sequelae, which significantly reduce the quality of life. We need new oral TB drugs that are more active and less toxic as well as new regimens with good efficiency and good tolerance both for drug-sensitive and drug-resistant TB [17, 20-26]. In particular, we need drugs that can reduce the duration of the treatment. Shorter regimens will improve patient adherence, reduce cumulative drug toxicities, and reduce clinics' workloads [18].

Table I. *The group classification of anti-TB drugs [20]*

Group	Characteristic	Drugs (abbreviations)
1	First-line anti-tuberculosis drugs used perorally	Isoniazid (INH), Rifamycin (RIF), Ethambutol (EMB), Pyrazinamide (PZA)
2	Injectable anti-tuberculosis drugs	Streptomycin (S), Kanamycin (Km), Amikacin (Am), Capreomycin(Cm), Viomycin (Vi)
3	Fluoroquinolones	Ciprofloxacin (Cfx), Ofloxacin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx), Gatifloxacin (Gfx)
4	Peroral bacteriostatic second-line anti-tuberculosis drugs	Ethionamide (Eto), Protionamide (Pro), Cycloserine (Cs), Terizidone (Trd), *Para*-aminosalicylic acid (PAS), Thioacetazone (Th)
5	Drugs with unknown mechanisms of action (not recommended by WHO for ordinary use to treat MDR TB)	Clofazimine (Cfz), Amoxycillin/clavulanate (Amx/Clv), Clarithromycin (Ctr), Linezolid (Lzd)

Table II. *Recommended daily dosage of anti-TB drugs for adults (mg) [21]*

Drug	Patient's weight		
	33-50 kg	51-70 kg	More than 70 kg (max.)
Isoniazid	300	300-600	600
Rifampicin	450	450-600	600
Pyrazinamide	1000-1500	1500-2000	2500
Amikacin	500-750	1000	1000
Ethambutol	800-1200	1200-1600	1600-2000
Levofloxacin	500	500-750	750-1000
Protionamid/ etionamid	500	750	750-1000
Capreomycin	500-750	750-1000	1000
Para-aminosalicylic acid	3000-5000	5000-8000	8000-12000
Cycloserin	500	500-750	750-100
Delamanid	100 mg twice daily taken with food, for 6 months		
Bedaquiline	400 mg once daily for the first 2 weeks and is then reduced to 200 mg three times weekly for the remaining 22 weeks		
Linezolid	600 mg once daily orally or intravenously		

New drug treatment options

Below we provide a brief characteristic of new and newly introduced old drugs for the treatment of UGTB.

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1. Nitroimidazoles. This group consists of novel anti-TB agents and may be used for TB caused resistant pathogen – both MDR and XDR. Nitroimidazoles act through inhibition of cell wall synthesis and oxidation, and include pretomanid and delamanid. Pretomanid is active against both replicating Mtb and persistors [27], but it is currently not licensed. Delamanid is however, approved by The European Medicines Agency for the treatment of MDR-TB in combination with other anti-TB drugs – but only if standard regimen cannot be used because of total drug resistance or intolerability.

2. Diarylquinolines. Bedaquiline is effective against M. tuberculosis both during active replication and in persistence. Bedaquiline has high activity against resistant pathogen – both MDR and XDR [28]. It has been the first new drug to be approved by the Food and Drug Administration (FDA) for the anti-TB therapy for more than 40 years [17]. Bedaquiline should not be used for monotherapy nowise. The polycomponent anti-TB therapy should include alongside with this new drug pyrazinamide and four second-line anti-TB drugs. However, if MDR and resistance to fluoroquinolones are found together, such a regimen is not appropriate [29]. Co-administration of bedaquiline and delamanid is not recommended due to the potential drug–drug interactions and possible cardiotoxicity [30, 31].

3. Oxazolidinones. Key point of the mechanism of action of linezolid is inhibition of protein synthesis. Linezolid is a first-generation oxazolidinone and has excellent oral bioavailability. Initially, oxazolidinones were approved for the therapy infections caused by of drug-resistant Gram-positive microbes. Severe neurological and haematological toxicity have limited widespread using of this class antibacterials [32,33].

For additional treatment tocopferol, canephron, and trospium chloride and selzink may be used [19]. Evaluation of the outcome of drug treatment of UGTB is difficult for several reasons. Identification of Mtb is not always possible before treatment and healing of kidney and prostate caverns is not possible at all. A special scale has therefore been suggested for the evaluation of the outcome of drug treatment [34].

BCG-induced UGTB

Bacillus Calmette–Guérin are live attenuated M. bovis. Normally, BCG is anti-TB vaccine, and from 1970 BCG is widely used for treatment of non-muscle invasive bladder cancer. BCG-therapy can be associated with complications as alive pathogen has long-time contact with defective urothelium. One of the most severe complication is BCG-induced UGTB, – mainly localized in the bladder or prostate. BCG-induced TB can develop in other systems, too, and even BCG sepsis has been reported in rare cases [35-38]. Diagnosis of BCG – induced bladder TB can be made according to clinical features such as significant dysuria and decreased bladder volume, but not by microbiology. Histological confirmation is crucial, but in about half of patients specific granulomas could not be found, only fibrotic and inflammatory changes occur.

For the treatment of BCG-induced UGTB a short course (2 months) of rifampicin, levofloxacin and isoniazid is recommended. Anti-TB therapy may be terminated in two months if the patient becomes symptom-free relief and urinalysis is normal. If dysuria and / or pyuria persists after 8 weeks, anti-TB treatment should be continued for another two months. The small contracted bladder is an indication for cystectomy or enterocystoplasty. The patient should receive anti-TB therapy for at least 2 months after surgery.

Patients with UGTB should be followed up every 6 months for 1-3 years for early diagnosis of relapse. Control intervals will depend on the type and stage of the disease. Specific prophylaxis against urogenital TB is currently not available.

Side effects of anti-TB drugs

Data on adverse events have not been evaluated globally owing to dissimilar reporting. The assessment of adverse events suggested a risk of excess hepatotoxicity with rifampicin + isoniazid combination. Drug-induced hepatotoxicity is not uncommon with anti-TB drugs. Linezolid is associated with anemia and thrombocytopenia, and care should be taken in patients with anemia. Concomitant use of drugs that prolong QTc should be avoided if possible – such drugs require extra vigilance and monitoring with electrocardiography if prescribed with bedaquiline and fluoroquinolones. CYP3A4 inhibitors and CYP3A4 inducers can interact with bedaquiline: CYP3A4 inhibitors include the azole antifungals (ketoconazole, voriconazole and itraconazole), and macrolide antibiotics other than azithromycin; the azole antifungals in general can safely be used for less than 2 weeks whereas fluconazole could potentially be used for more than 2 weeks.

Monthly examination should be performed for the control of the results of the therapy and estimation of possible indication for surgery.

Conclusions

Urogenital TB is difficult to diagnose as early disease is often asymptomatic. The index of suspicion on UGTB is low, so the correct diagnosis is delayed. Complicated forms of UGTB show with delayed diagnosis may be difficult to treat with standard anti-TB therapy, while in-time diagnosed “minor” forms may be cured by medicines without surgery. Even if we have a case of early diagnosed UGTB, non-optimal therapy may result in over-fibrosis, scarring and strictures of urinary tract, which, again, are an indication for surgery. Nevertheless, we have enough anti-TB drugs to cure UGTB.

Key points

1. Forms of UGTB have different clinical characteristics. Each form requires tailored antibiotic therapy and management.
2. If untreated, two-thirds of newly revealed TB patients will die, and the remaining one-third is likely to suffer from serious sequelae.

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3. Inappropriate therapy may lead to development of overfibrosis, that result in the development of ureteral stricture.
4. Anti-TB therapy should be multi-component, continuous, long-time and controlled.
5. Treatment of UGTB differs from the therapy of pulmonary TB.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflicts of interest.

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