Urogenital Tuberculosis: Classification, Diagnosis, and Treatment

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Article info

Abstract

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Urogenital tuberculosis (TB) is one of the most common forms of extrapulmonary TB. There are many controversies concerning the epidemiology, definition, classification, treatment, and management of patients with urogenital TB, which includes kidney TB, urinary tract TB that is a complication of kidney TB, and genital TB, both male and female. In this paper, we discuss the risk factors and a detailed classification for urogenital TB and the clinical features of each form of the disease. Special attention is paid to urogenital TB induced by bacillus Calmette-Guérin. Modern approaches to the diagnostic work-up and chemotherapy of urogenital TB are described.

Patient summary: Urogenital tuberculosis (TB) seems to be a rare disease, but it is mostly overlooked. Urogenital TB is contagious and is a cause of infertility. Modern techniques allow diagnosis of this infection in time, and optimal management may save organs.

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1. Introduction

According to the World Health Organization reports reviewed in March 2014, about one-third of the world’s population has latent tuberculosis (TB), which means people have been infected by Mycobacterium tuberculosis (Mtb) but are not yet ill with the disease and cannot transmit the disease [1]. People infected with Mtb have a lifetime risk of falling ill with TB of 10%. However, persons with compromised immune systems, such as people with human immunodeficiency virus (HIV), malnutrition, or diabetes mellitus or people who use tobacco, have a much higher risk of becoming ill [1].

TB is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2012, 8.6 million people became ill with TB and 1.3 million died from TB. It is a leading killer of people living with HIV and a cause of one-fifth of all deaths [1].

In 2012, the largest number of new TB cases occurred in Asia, accounting for 60% of new cases globally. Despite major efforts to increase detection, an estimated third of new TB cases is still missed each year. The unavailability of a rapid, low-cost, accurate diagnostic assay that can be used at the point of care is a major hindrance [1]. Urogenital TB is a frequent form of TB but is mostly overlooked. Very few multicenter randomized studies on urogenital TB have been conducted, mainly because of unclear diagnostic criteria and treatment recommendations.

2. Classification

2.1. Terms and definitions

The first note on urogenital TB was made by Porter in 1894 [2]. In 1937, Wildbolz [3] suggested the term genitourinary TB. However, the term urogenital TB is more correct because kidney TB, which is usually primary, is diagnosed more often than genital TB.

Urogenital TB refers to an infectious inflammation of any urogenital organ, isolated or in combination (kidney,
urinary tract, and/or male or female genitals), caused by *Mtb* or *Mycobacterium bovis*.

Genital TB is an infectious inflammation of the female or male genitals comprising female or male genital TB caused by *Mtb* or *M. bovis*.

Kidney TB refers to infectious inflammation of the kidney parenchyma caused by *Mtb* or *M. bovis*.

Urinary tract TB is an infectious allergic inflammation of the upper and/or lower urinary tract caused by *Mtb* or *M. bovis*, always secondary to kidney TB, and should be considered a complication of kidney TB.

Female genital TB is not included in this paper.

### 2.2. Etiology of urogenital tuberculosis

There is a big family of *Mycobacteria*, but not all members of this family are pathogenic for humans. *Mtb* and *M. bovis* are combined in the mycobacterial complex and are obligatory pathogens for the human organism. In a few instances, *M. africanum* may replace *M. bovis*. In 80–95% of cases, urogenital TB is caused by *Mtb*, but *M. bovis* is also an etiologic agent of TB [4–6] because TB is an anthropopozoonotic infection.

Bacillus Calmette-Guérin (BCG), which is in fact an attenuated *M. bovis*, is widely used for therapy of superficial bladder cancer. In some instances BCG therapy may be complicated by iatrogenic BCG-induced urogenital TB, mainly bladder or prostate TB, but in rare cases BCG sepsis is also possible [7–10].

### 2.3. Risk factors for urogenital tuberculosis

The main route of infection is via hematogenous and lymphatic spread, but direct extension from infected urine and ejaculate is also possible. Urogenital TB has several risk factors, clinical signs, and symptoms:

- Contact with TB infection (eg, TB-infected patients or animals, infected pathologic material in the laboratory)
- TB of any other localization, whether active or cured, especially in disseminated forms
- Urinary tract infection (UTI) with frequent recurrences and resistance to standard therapy
- UTI with persistent dysuria and decreasing bladder volume
- Sterile pyuria
- Leucocytes in all portions of a three-glass test in a patient with epididymitis or orchiepididymitis
- Pyospermia and/or hematospermia
- Scrotal, perineal, and lumbar fistulas

Patients with such risk factors, signs, and symptoms suspicious for urogenital TB should be evaluated carefully.

### 2.4. Epidemiology of urogenital tuberculosis

Before anti-TB drugs were available, urogenital TB was an extremely frequent disease: Every fifth patient treated in urologic departments in France had kidney TB, and more than one-third of all people with pyonephrosis had TB etiology [11]. Now urogenital TB is the second most common form of TB in countries with a severe epidemic situation and the third most common form in regions with a low incidence of TB. The percentage of urogenital TB among extrapulmonary TB is 33.7–45.5%. More than 50% of patients with male genital TB also have pulmonary TB and/or kidney TB, but isolated forms are also possible. Often both the epididymis and prostate are involved. In developed countries, 2–10% of pulmonary TB patients also have urogenital TB [12,13]. In 20% of pulmonary TB patients, urogenital TB develops later, after recovery from the first infection [14]. In Russia, TB of the bone and joints and urogenital TB have about an equal frequency now [15]. A large proportion of all patients with urogenital TB are probably never diagnosed.

### 2.5. Presentation forms of urogenital tuberculosis

Urogenital TB includes many forms of TB with its own clinical features, each requiring specific therapy and management; therefore, correct clinical classification and staging are important for optimal management and therapy [16]. Urogenital TB can be subclassified depending on the organ affected. TB of the kidney and bladder is categorized into four stages according to the extent of tissue destruction.

Kidney TB is staged as follows: Stage 1 is TB of kidney parenchyma (KTB-1; nondestructive form), stage 2 is TB papillitis (KTB-2; small destructive form), stage 3 is cavernous kidney TB (KTB-3; destructive form), and stage 4 is polycavernous kidney TB (KTB-4; widespread destructive form).

Urinary tract TB includes TB of the renal pelvis, ureter, bladder, and/or urethra and is always a complication of kidney TB.

TB of the bladder is staged as follows [16,17]: Stage 1 is tuberculosis-infiltrative bladder TB, stage 2 is erosive-ulcerous bladder TB, stage 3 is spastic cystitis (ie, overactive bladder), and stage 4 is contracted bladder up to full obliteration.

Male genital TB is subclassified according to the organs affected: TB epididymitis (unilateral or bilateral), TB epididymo-orchitis (unilateral or bilateral), TB of the prostate (infiltrative or cavernous forms), TB of the seminal vesicles, or TB of the penis.

BCG-induced urogenital TB develops as a complication of BCG therapy for bladder cancer and is considered a separate type of bladder TB. Instillation of BCG causes specific inflammation of the bladder mucosa that kills cancer cells by a controlled temporary local inflammation. Loss of control may result in spread of infection. Systemic dissemination of bacilli may lead to development of generalized BCG-induced TB when all organs including the meninges are involved in TB inflammation. Among the urogenital complications of BCG therapy, bladder TB is the most common; TB epididymo-orchitis and TB of the penis are rare. BCG-induced granulomatous prostatitis has been reported to occur in at least 41% of patients after BCG immunotherapy [18]. In most of these cases, patients are asymptomatic and only rarely (0.9–1.3%) have clinical complaints, palpable induration of the prostate, or an
elevated prostate-specific antigen [19]. BCG-induced prostatitis does not require any therapy unless it becomes clinically significant [20].

2.6. Complications of urogenital tuberculosis

Complications of kidney TB are chronic renal failure, fistula, and high blood pressure. Complications of male genital TB are strictures, fistula, infertility, and sexual dysfunction.

3. Clinical features

Clinical features of urogenital TB are nonspecific and unstable and depend on many factors, which is one of the reasons for the late diagnosis. As a whole, kidney TB patients complain of flank pain (up to 80%) and/or dysuria (up to 54%). If the urinary tract is involved, renal colic (24%) and gross hematuria (up to 20%) may occur. Prostate TB manifests as by perineal pain and dysuria and in half of the cases by hematospermia. TB epididymo-orchitis always starts from epididymitis; isolated TB orchitis does not exist. Edema swelling and pain of the scrotal organs are most often the first symptoms. In 68% of cases, there is an acute debut of the disease. In 32–40% of patients, the disease has a chronic or asymptomatic course [15,16,21,22].

3.1. Kidney tuberculosis

KTB-1 presents with a minimal lesion without destruction. Intravenous urography (IVU) is normal. Urinalysis is often normal in children, but low-level leukocyturia may be found in adults. Detection of Mtb in urine is always necessary for diagnosing KTB-1. Usually patients have no complaints and are diagnosed by chance. The prognosis is good. Usually the outcome is a full recovery, and complications are rare. Most often Mtb in KTB-1 patients is sensitive to anti-Tb drugs. KTB-1 may be fully cured with anti-TB drugs. However, with inappropriate therapy, KTB-1 may progress to a destructive form.

KTB-2 may also be cured with anti-TB drugs only. If KTB-2 is complicated by urinary tract TB, reconstructive surgery may be indicated. Prognosis is good, but recovery with fibrous deformation and post-TB pyelonephritis is common. With inappropriate therapy, KTB-2 may progress to the next stage. Mtb may be resistant to anti-TB drugs but is not detected in all cases.

KTB-3 may develop in two ways: from TB of the parenchyma or from papillitis (KTB-2). The first way means development of a subcortical cavern without connection to the collecting system. The clinical manifestation is similar to a renal carbuncle; hence the diagnosis is usually made after the operation. The second way is the destruction of a papilla until a cavern develops. Complications develop in more than half of the patients. Full recovery with anti-TB drugs only is impossible, and surgery is indicated in most cases. The best outcome is the formation of a sterile cyst; the worst outcome is further destruction into polycavernous TB.

KTB-4 means several caverns in the kidney, although overall renal function may still be sufficient. KTB-4 may result in fistulas secondary to pyonephrosis, but self-recovery is possible by total calcification of a kidney. This mechanism occurs if a stricture of the ureter blocks the kidney drainage and caseation in the caverns is impregnated by calcium, the so-called auto-amputation of the kidney. KTB-4 is almost always complicated, and very often the contralateral kidney is also involved. Recovery with anti-TB drugs only is impossible. Surgery is always necessary; the most common intervention is nephrectomy. Figures 1 and 2 show some examples of stage 4 kidney TB.

Urinary tract TB is a specific complication of kidney TB and always secondary to it. Urinary tract TB first appears as an edema. The next stages are infiltration, ulceration, and fibrosis.

TB of the ureter usually develops in the lower third, but multiple lesions are also possible. Incorrect therapy may lead to development of a ureteral stricture that may result in loss of the kidney, even if the kidney TB was ultimately cured.

**Fig. 1** – Computed tomography scan of tuberculosis (TB) of the right kidney showing stage 4 kidney TB and TB of the right ureter and stage 4 bladder TB.

**Fig. 2** – Computed tomography of tuberculosis (TB) of the bilateral kidney showing stage 4 kidney TB.
3.2. **Bladder tuberculosis**

The main symptom of bladder TB is frequency, urgency, and hematuria. The first two stages should be treated with standard anti-TB drugs only; the third stage is treated with standard anti-TB drugs and troleandomycin. Cystectomy is indicated in the fourth stage. TB of the urethra is currently a rare complication and is usually diagnosed at the stage of a stricture; then reconstructive surgery is indicated. KTB-4 is complicated by bladder TB. Figure 3 shows an example of stage 4.

BCG-induced bladder TB (complication of BCG therapy for bladder cancer) may be diagnosed by clinical features such as significant dysuria, decreased bladder volume, and pyuria presenting about 3 wk after the instillation of BCG. TB involvement of the detrusor is the clinical background of the symptoms. Diagnosis depends on histology, not bacteriology; however, in about 50% of cases, only fibrosis and inflammation may be found in the biopsies. Microbiology is not helpful.

3.3. **Male genital tuberculosis**

TB epididymitis may be unilateral or bilateral. Bilateral TB epididymitis is always secondary to prostate TB. Isolated TB epididymitis was an incidental histologic finding in 22% of patients undergoing surgery for acute nonspecific epididymitis [16,23,24].

TB of the testis is always secondary to infection of the epididymis, which in most cases is blood-borne because of the extensive blood supply of the epididymis, particularly the lobus minor. In 62% of patients with epididymo-orchitis, kidney TB is diagnosed as well. Every third patient has bilateral lesions. The disease is complicated by fistulas in about 12% of cases [16,23,24].

TB of the prostate is often an underdiagnosed disease. Three-quarters of men dying from all forms of TB had prostate TB on autopsy. Most cases were not diagnosed in vivo [25]. Prostate TB is important for several reasons: (1) It may be a sexually transmitted disease, and up to 50% of pulmonary TB patients have *Mtb* in their ejaculate if they are comorbid with hepatitis and syphilis [26,27]; (2) it leads to infertility; (3) it causes chronic pelvic pain like any other type of prostatitis and a significant reduced quality of life [28]; and (4) it impairs sexual function, thereby further reducing quality of life [29]. In 79% of cases, prostate TB was accompanied by kidney TB and in 31% by TB epididymo-orchitis. Only 5% of all prostate TB patients had prostate TB as the sole manifestation of TB infection [16,29,30]. Caverns of the prostate cannot be cured and remain intact, with a high predisposition to relapse [16,29,30].

TB of the seminal vesicles is secondary to prostate TB and leads to infertility. Because drainage of the caseous ejaculate is difficult, TB of the seminal vesicles tends to calcify [31].

TB of the penis presents as ulcers on the glans or penile skin. The condition is very rare, but it can occur after sexual intercourse with infected women or via a direct infection through a penile wound during ritual circumcision [32,33]. Currently it is mainly a complication of BCG therapy [34,35].

4. **Physical examination**

Special attention should be paid to any fistula. Scrotal and perineal fistulae are highly suspicious for TB [36]. In the acute course of TB epididymitis, a hard, painful enlarged epididymis intimately welded with the testis can be palpated. In chronic cases, the epididymis is still hard, enlarged, and painless but usually with a clear border to the testis. In 35–40% of cases, the findings are bilateral. Digital rectal examination of the patient with prostate TB shows a moderate enlarged tuberous prostate with weak pain [37,38].

5. **Laboratory tests**

As a rule, all patients with genital TB should be screened for chest and upper urinary tract involvement and HIV infection.

5.1. **Urinealysis and culture tests**

Leukocyturia is found in 90–100% of patients with kidney TB and hematuria in 50–60% [16]. Before the antibiotic era, sterile pyuria was a specific sign of kidney TB, but now up to 75% of patients have nonspecific pyelonephritis alongside kidney TB, and therefore common urinary tract pathogens and *Mtb* may be found in the urine together [37–39]. To diagnose a common UTI, a bacterial growth of at least 10^4 CFU/ml is needed, but even one single *Mtb* is evidence for the presence of urogenital TB [16]. The diagnosis of urogenital TB is absolutely confirmed when *Mtb* is detected, but in recent years, *Mtb* could be found in only half of TB patients. Therefore, in patients suspected of having urogenital TB, but without documented evidence of *Mtb*, the diagnosis of urogenital TB has to be made on the basis of other features, such as a skin test, histologic findings, caverns revealed by intravenous pyelography, or sterile pyuria [16].

At least three, but preferably five, serial microbiologic studies with urine (including postejaculate and postmassage...
Table 1 – Spectrum of bacteriologic methods for diagnosing urogenital tuberculosis

<table>
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<tr>
<th>Method</th>
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<tr>
<td>Direct smear microscopy (Ziehl-Neelsen stain)</td>
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<td>Luminescent microscopy</td>
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<td>Solid culture methods (Lowenstein-Jensen, Finn-2 medium)</td>
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<tr>
<td>Liquid culture methods (medium Middlebrook 7H9; commercial broth-based culture systems detect TB bacteria, Bactec MGIT (Becton, Dickinson and Company, Franklin Lakes, NJ, USA))</td>
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<tr>
<td>Polymerase chain reaction</td>
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<tr>
<td>Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance (GeneXpert MTB/RIF; Cepheid, Sunnyvale, CA, USA)</td>
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<tr>
<td>Immune-ferment analysis enzyme-linked immunospot</td>
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<tr>
<td>Interferon-gamma release assay</td>
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<tr>
<td>Isothermal microcalorimetry</td>
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TB = tuberculosis.

5.2. Provocative tests

The Mantoux test is positive in >90% of TB patients, but it has no value in regions with a severe epidemic situation (e.g., China, Russia, India, and Pakistan), where almost all adults are infected with MTB and thus all have a positive skin tuberculin test. The new Diaskintest (Stragen Pharma SA, Geneva, Switzerland) has high specificity but low sensitivity, and it is not recommended for the diagnosis of urogenital TB. A subcutaneous tuberculin provocative test is recommended, especially in cases where the diagnostic work-up is difficult [30].

5.3. Histology

Histologic investigation may reveal epithelioid granuloma or caseous necrosis, both of which are soon replaced by fibrous tissue, especially after suboptimal previous therapy. If the patient was treated with fluoroquinolones and amikacin for a common UTI, which masks urogenital TB, the specific histologic changes transform into fibrosis, and pathomorphologic confirmation of the disease becomes impossible. In isolated external genital TB without renal and prostate involvement, diagnosis of male genital TB is often only possible by histologic examination.

Prostate biopsy should only be performed after urethrogramy to exclude caverns. Prostate biopsy specimens should be investigated by histology and bacteriology, at least by polymerase chain reaction [29,30,40].

Fine-needle aspiration cytology may be useful to diagnose TB of the external male genital [30]. However, scrotal surgery including histology should always be considered if there is suspicion that the mass is malignant. Fatal complications due to fulminant generalization of TB have occurred after biopsies performed in nontreated patients with active urogenital TB.

6. Imaging

6.1. Ultrasonography

Renal ultrasound may give indirect evidence of urogenital TB only. Because prostate TB is accompanied by kidney TB in 79% of cases [15,16], pathologic findings detected by renal ultrasound in patients with so-called chronic prostatitis are very suspicious for urogenital TB. TB epididymitis and orchitis present as diffusely enlarged lesions that may be homogeneous or heterogeneous and can also occur as nodular enlarged heterogeneously hypoechoic lesions [41]. Transrectal ultrasound may reveal hypo- and hyperechoic lesions of the prostate, predominantly in the peripheral zone, but also as prostatic lithiasis, which in fact may be calcified zones of TB inflammation [27,41].

6.2. Radiologic examinations

Radiologic examinations are not useful for the diagnosis of urogenital TB in early stages before development of tissue destruction. The radiologic investigations indicated for patients suspected of urogenital TB are plain x-ray films of the urinary tract that may detect calcifications in the kidney regions and in the lower urogenital tract. Intravenous pyelography (IVP) is indicated for patients with leukocyturia and/or abnormalities on ultrasound investigations. Retrograde urethrography should be performed in all patients with genital TB to exclude caverns in the prostate. X-ray examination is very useful to detect cavernous forms of urogenital TB, both in kidney TB (IVP) and prostate TB (urethrography), but multislice computed tomography (CT) is significantly more informative. For cavernous prostate tuberculosis, retrograde urethrography is crucial for the diagnosis. On a contrast-enhanced CT scan, TB of the prostate or seminal vesicles can be seen as low-density or cavitation lesions due to necrosis and caseation with or without calcification. Without calcification, the findings may be similar to pyogenic prostatic abscesses [42,43]. Urogenital TB in the early stages, however, has no specific radiologic characteristics.

6.3. Endoscopy

Instrumental interventions are generally of limited value for the diagnostic work-up in urogenital TB. However, cystoscopy is indicated in all urogenital TB patients with dysuria. Persistent dysuria in a kidney TB patient is suspicious for bladder TB, even without histologic confirmation, which may be obtained in only 12% of the patients with stage 4 bladder TB [16,44]. Any mucosal pathology should be biopsied and investigated both by histology and bacteriology, although the absence of specific findings does not exclude the diagnosis of TB. Ureteropyeloscopy may incidentally reveal TB ulcers, especially when the procedure is performed in patients with renal colic because of roentgen-negative stones.
7. Therapy ex juvantibus

If the patient is suspected of having urogenital TB but there is no evidence of Mtb on culture or histology and the tuberculin provocative test and X-ray imaging are unconvincing, the clinical diagnosis of urogenital TB has to be made on the basis of therapy ex juvantibus, which is subclassified into two types according to the level of suspicion. Therapy ex juvantibus of the first type is indicated in patients with a low suspicion for urogenital TB. Antibiotics that do not inhibit Mtb (fosfomycin, cephalosporins, and nitrofurantoin) are prescribed, and resolution of clinical symptoms allows excluding the diagnosis of urogenital TB. If there is still doubt about the etiology of a UTI, therapy ex juvantibus of the second type is indicated. It includes two to four antibiotics that inhibit only Mtb but do not affect the usual uropathogens (isoniazid, para-aminosalicylic acid [PAS], protonamide, ethionamide, ethambutol, and pyrazinamide). A positive result within 2 mo allows establishing the diagnosis of urogenital TB [30].

In patients with a high risk of urogenital TB, the diagnosis can be made on the basis of a skin test, the histologic picture, caverns revealed by urography, and sterile pyuria in the absence of clinical symptoms [16,30].

8. Treatment

8.1. Chemotherapy

The principles of anti-TB chemotherapy are continuity, compliance, and succession of the treatment. The patient must take a minimum of four anti-TB drugs simultaneously for a minimum of 6 mo, depending on the form of urogenital TB. Neglect of these principles leads to development of drug-resistant Mtb and relapse of TB. Table 2 presents the classification of the anti-TB drugs.

When the disease is naive and caused by drug-sensitive Mtb, first-line anti-TB drugs should be prescribed. When there is resistance of Mtb to first-line anti-TB drugs or poor tolerance, severe adverse effects, and recurrence of the disease, second- or third-line anti-TB drugs are indicated.

Table 2 – Classification of antituberculosis drugs

<table>
<thead>
<tr>
<th>First-line anti-TB drugs (basic)</th>
<th>Second-line anti-TB drugs (reserve)</th>
<th>Third-line drugs for special clinical situations</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td>Protionamide/Ethionamide</td>
<td>Amoxicillin/clavulinate</td>
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<tr>
<td>Rifampicin</td>
<td>Kanamycin</td>
<td>Meropenem</td>
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<tr>
<td>Pyrazinamide</td>
<td>Amikacin</td>
<td>Imipenem</td>
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<tr>
<td>Streptomycin</td>
<td>Capreomycin</td>
<td>Clarithromycin</td>
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<tr>
<td>Ethambutol</td>
<td>Cycloserine</td>
<td>Linezolid</td>
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<tr>
<td>Rifabutin</td>
<td>Para-aminosalicylic acid</td>
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<tr>
<td>Fluoroquinolones</td>
<td>Bedaquiline</td>
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<td>Perazine</td>
<td>Terizidone</td>
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TB = tuberculosis.

8.2. Etiotropic therapy

The treatment of urogenital TB differs from the treatment of pulmonary TB. Streptomycin and kanamycin are not recommended for urogenital TB. Ofloxacin and levofloxacin are the only fluoroquinolones suitable to treat urogenital TB. Moxifloxacin and sparfloxacin are respiratory fluoroquinolones that are suitable for pulmonary TB but not optimal for urogenital TB. PAS is recommended for urogenital TB with involvement of the pelvic organs because it provides an antiprostaglandin, anti-inflammatory effect [16]. Amoxicillin/clavulanate should be prescribed together with meropenem or imipenem because they potentiate the anti-TB effect. Cycloserine is recommended if the patient has significant comorbidity and a nonspecific UTI [16]. Patients with urogenital TB and HIV who are receiving antiretroviral therapy should be treated with rifabutin instead of rifampicin. Rifampicin and streptomycin are contraindicated in patients after organ transplantation. Amikacin, streptomycin, and kanamycin are contraindicated for urinary tract TB patients because these drugs provoke a transformation from TB inflammation to fibrosis [16].

Five regimens of chemotherapy are used depending on the form of urogenital TB. Table 3 presents the standard regimens of anti-TB treatment. Regimen 1 is applied in newly diagnosed treatment-naïve patients with drug-susceptible (or if there was no growth of Mtb) uncomplicated kidney TB stages 1 and 2, isolated TB epididymitis, patients who were diagnosed by histology after organ removal, and if there is no other TB focus. Regimen 2 is applied in newly diagnosed treatment-naïve patients with drug-susceptible (or if there was no growth of Mtb) uncomplicated kidney TB stages 3 and 4. Regimen 3 is applied in newly diagnosed treatment-naïve patients with drug-susceptible (or if there was no growth of Mtb) kidney TB stage 4, kidney TB of any stage complicated by urinary tract TB, and prostate TB. Regimen 4 is applied in patients with relapse of urogenital TB, with high risk of multidrug resistance (MDR), independent of form and stage. Regimen 5 is applied in patients with MDR urogenital TB, independent of form and stage.

Every regimen starts with a phase of intensive therapy (2–4 mo) followed by the continuation phase (Table 3). The dosage of anti-TB drugs depends on the patient’s weight. Recommendations are given in Table 4.

Anti-TB drugs may be administered orally, but parenteral administration is preferred because it provides better compliance and has fewer side effects. Intravenous infusion is optimal. Short-term treatment for 6–9 mo is suitable in uncomplicated cases in regions with a low incidence of TB. In complicated cases (relapse, immunosuppression, drug resistance) and in regions with epidemic TB, anti-TB therapy should be given for up to 9–14 mo with four to five drugs. MDR TB should be treated with at least five anti-TB drugs for at least 18 mo.

8.3. Supplemental therapy

Supplemental therapy is prescribed to minimize the negative consequences of anti-TB chemotherapy, to prevent...
excessive development of fibrosis, to decrease toxicity, to save the function of an organ, and to improve healing. Examples of medications for the supplemental treatment of urogenital TB are tocoferol, canephron, and trospium chloride for bladder TB stage 3 and afala and prostanorm for prostate TB [16,17,27].

9. Bacillus Calmette-Guérin–induced urogenital tuberculosis

BCG-induced bladder TB should be treated with two or three anti-TB drugs for 2–4 mo if bladder volume is normal. If microcystitis has developed, a cystectomy is indicated, but anti-TB chemotherapy is also needed. BCG-induced bladder TB should be treated with daily doses of rifampicin 0.6 g and isoniazid 0.6 g for 2 mo. If there is growth of nonspecific bacteria in the urine, levofloxacin 0.5 g daily should also be prescribed. If symptoms resolve within 8 wk and urinalysis is normal, the anti-TB therapy can be terminated. If urodynamics have improved after 8 wk but the patient is not fully recovered, anti-TB therapy should be continued for another 2 mo. If there is no clinical resolution and bladder volume remains <100 ml after 8 wk of treatment with rifampicin and isoniazid, a cystectomy (in male patients a cystoprostatectomy) is indicated. Treatment with rifampicin, isoniazid, and levofloxacin should be continued for at least 2 mo after surgery until complete recovery indicated with a normal urinalysis.

BCG instillation is contraindicated in patients who develop dysuria and leukocyturia. Nonsteroidal anti-inflammatory drugs and nitrofurantoin or fosfomycin for 3–5 d should be prescribed in this case. BCG therapy may be continued only when symptoms of cystitis have improved. BCG vaccine should not be given as an attempt to prevent this complication at the time of cystitis. A scheduled BCG regimen should not be resumed after recovery of BCG-induced TB.

Patients with BCG-induced epididymo-orchitis should be treated with rifampicin 0.6 g plus isoniazid 0.6 g and levofloxacin 0.5 g daily for 2 mo. Patients with symptomatic BCG-induced prostatitis should be treated with rifampicin 0.6 g plus isoniazid 0.6 g and levofloxacin 0.5 g daily for 4–6 mo until resolution of symptoms. Epididymo-orchectomy is indicated in case of abscess formation. Patients should be seen for a control examination every 6 mo for 2 yr. Clinically insignificant BCG-induced mycobacterial prostatitis does not always require anti-TB therapy, but close monitoring and information about the risk of sexual transmission is necessary [18–20]. Figure 4 presents an algorithm for the management of BCG-induced TB.

<table>
<thead>
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<th>Table 3 – Standard regimens of chemotherapy for urogenital tuberculosis</th>
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<td><strong>Regimen</strong></td>
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</tbody>
</table>

Amx = amoxicillin/clavulanate; Cap = capreomycin; Clr = clarithromycin; Cs = cycloserine; E = ethambutol; H = isoniazid; Imp = imipenem; Mp = meropenem; Off/Lef = ofloxacin/levofloxacin; PAS = para-aminosalicylic acid; Pt(Et) = pyrithione (ethionamide); R = rifampicin; Rb = rifabutin; Z = pyrazinamide.

Table 4 – Recommended daily dosage (in milligrams) of antituberculosis drugs for adults

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Patient weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>33–50 kg</td>
<td>51–70 kg</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>300–450</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>300</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1000–1500</td>
</tr>
<tr>
<td>Amikacin</td>
<td>500–750</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>800–1200</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400–800</td>
</tr>
<tr>
<td>Prothionamide/Ethionamide</td>
<td>500</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>500–750</td>
</tr>
<tr>
<td>PAS</td>
<td>3000–5000</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>500</td>
</tr>
</tbody>
</table>

PAS = para-aminosalicylic acid.

10. Surgery

Like any other UTI, urogenital TB may be cured by chemotherapy alone if diagnosed in time. However, surgical intervention is indicated in advanced cases and for the correction of complications (urinary tract TB). Table 5 lists the most relevant surgical interventions.

All surgical interventions should be performed under the coverage of anti-TB therapy. Treatment duration is estimated after histologic investigation of the removed tissue [44–46].

11. Follow-up and prevention of relapse

Patients with urogenital TB should be followed up for control or eradication if symptoms persist or recur after...
completion of the therapy. Patients should be seen every 6 mo for 1–3 yr, depending on the form and stage of the disease. To prevent relapse in patients with complicated urogenital TB, a repeated short course (for 2 mo) of therapy with isoniazid and rifampicin is recommended. In case of MDR-urogenital TB, the preventive therapy is prescribed according to the sensitivity of Mtb. No specific prophylaxis is available for urogenital TB.

**Conflicts of interest**

The authors have nothing to disclose.
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References


