Chapter 11
Urogenital Tuberculosis

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Take-Home Message
Urogenital tuberculosis (TB) seems to be a rare disease, but it is mostly overlooked. Urogenital TB is contagious and it is a reason for infertility. Modern techniques allow diagnosing this infection in time, and optimal management may save organs.

11.1 History

The first note on urogenital tuberculosis (TB) was made by Porter in 1894 [1]; this time the term "urogenital TB" was accepted. In 1937 Wildbolz [2] suggested the term genitourinary TB. There was no particular reason to change the term, nevertheless the medical society approved the new term and since we had both terms. However, the term urogenital TB is more correct, because kidney TB, which is usually primary, is diagnosed more often than genital TB.

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11.2 Definitions

Urogenital TB (UGTB) may be defined as an infectious inflammation of any urogenital organ (kidney, urinary tract, and/or male or female genitals), caused by *Mycobacterium tuberculosis* (Mtb) or *Mycobacterium bovis* (*M. bovis*).

Genital TB (GTB) may be defined as an infectious inflammation of the female or male genitals, caused by *Mtb* or *M. bovis.*

Urinary tract TB (UTTB) is an infectious-allergic inflammation of the upper and/or lower urinary tract, always secondary to kidney TB (KTB) and should be considered a complication of KTB.

Female genital TB is not included in this chapter.

11.3 Classification

UGTB can be classified into the following entities:

11.3.1 Kidney Tuberculosis (KTB)

The infectious inflammation of the kidney parenchyma, caused by Mtb or *M. bovis* There are four stages to be considered:

Stage 1: TB of kidney parenchyma (nondestructive form, KTB-1) is subject to conservative therapy only. KTB-1 has minimal lesion without destruction and full recovery is possible by anti-TB drugs. Intravenous urography (IVU) is normal. Urinalysis in children is often normal, but in adult low-level leukocyturia may be found. Usually patients have no complaints and are diagnosed accidentally. Mtb detection in urine is always necessary for diagnosing kidney TB stage 1.

Stage 2: TB papillitis (small-destructive form, KTB-2) may be uni- and bilateral, solitary, and multiple. KTB-2 should be treated with anti-TB drugs, but if complicated, reconstructive surgery is indicated. Mtb is not detected in all cases and may be resistant.

Stage 3: Cavernous kidney TB (destructive form, KTB-3). KTB-3 has two ways of pathogenesis, from TB of parenchyma or from papillitis. The first way means development of a subcortical cavern without connection to the collecting system. The clinical manifestation of a subcortical cavern is similar to a renal carbuncle; thus the diagnosis is usually made after the operation. The second way is the destruction of the papilla until a cavern is developed. Complications develop in more than half of the patients. Full recovery by anti-TB drugs is impossible, and surgery is generally indicated.

Stage 4: Polycavernous kidney TB (widespread-destructive form, KTB-4). Recovery with anti-TB drugs only is impossible; surgery is necessary, basically nephrectomy.

Complications of kidney TB are chronic renal failure, fistula, and high blood pressure.

11.3.2 Urinary Tract TB (UTTB)

Urinary tract TB (UTTB) includes TB of renal pelvis, ureters, bladder, and urethra. UTTB first appears as an edema; the next stages are infiltration, ulceration, and fibrosis. UTTB is always secondary to KTB. UTTB can be subclassified in the following parts:

11.3.2.1 TB of Ureter

TB of the ureter usually develops in the lower third, but multiple lesions are possible too.

11.3.2.2 TB of the Bladder

TB of the bladder is divided into four stages [3]:

Stage 1 – tubercle-infiltrative
Stage 2 – erosive-ulcerous
Stage 3 – spastic cystitis, which in fact means overactive bladder
Stage 4 – contracted bladder up to full obliteration

The first two stages should be treated by standard anti-TB drugs, the third stage with standard anti-TB drugs and trospium chloride, and the fourth stage is indicated for cystectomy with urine diversion or bladder replacement surgery.

There is one more form of bladder TB, the iatrogenic BCG-induced bladder TB, which develops as a complication of BCG therapy for bladder cancer.

11.3.2.3 TB of Urethra

TB of the urethra is nowadays not a frequent complication; usually it is diagnosed at the stage of a stricture.

11.3.3 Male Genital Tuberculosis (MGTB)

Male genital tuberculosis (MGTB) is subdivided into four categories:

11.3.3.1 TB Epididymitis (Uni- or Bilateral)

Bilateral TB epididymitis is always secondary to prostate TB. Isolated TB epididymitis was found in 22% as accidental surgical finding [4].

11.3.3.2 TB Orchiepididymitis (Uni- or Bilateral)

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 orchiepididymitis, KTB is diagnosed as well. Every third patient has bilateral lesions. In about 12% of cases, the disease is complicated by fistulas [4, 5].

11.3.3.3 TB of the Prostate (Infiltrative or Cavernous Forms)

Prostate TB is an often underdiagnosed disease. Three-quarters of men, who died from any form of TB, had prostate TB which was mostly overlooked until autopsy [6]. In 79% of patients, prostate TB was accompanied by KTB, in 31% by TB orchiepididymitis, and in 5% an isolated prostate TB was diagnosed [3–5].

11.3.3.4 TB of Seminal Vesicles

TB vesiculitis is secondary to prostate TB and leads to infertility. As drainage of caseous ejaculate is difficult, TB of seminal vesicles exhibits a tendency to calcification.

11.3.3.5 TB of the Penis

Penile TB is rare but can occur after sexual intercourse with infected females [7] or via a direct infection through a penile wound during ritual circumcision. Penile lesions present as ulcers on the glans or penile skin. Also it may be as a complication of BCG therapy [8].

11.3.3.6 Complications of MGTB

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

11.3.4 Generalized Urogenital Tuberculosis (gUGTB)

Generalized urogenital tuberculosis (gUGTB) simultaneous lesions of the kidney and the urinary and genital organs; gUGTB is always considered a complicated form of TB.

Etiology of Urogenital TB
In a big family of *Mycobacteria*, *Mtb and M. bovis* are combined in the *mycobacterial complex* and are obligatory pathogens for the human organism. In 80–95% of cases UGTB is caused by Mtb, but as TB is an anthropozoonotic infection, *M. bovis* is also an etiological agent of TB [9–11]. Bacillus Calmette-Guérin (BCG), which is in fact an attenuated *M. bovis*, is widely used for therapy of superficial bladder cancer. BCG therapy may be complicated by iatrogenic BCG-induced UGTB – mainly bladder or prostate TB – but in rare cases BCG sepsis has been diagnosed [12–15].

11.4 Diagnosis

11.4.1 Clinical Features

Clinical features of UGTB are non-specific and instable and depend on many factors. This is one of the reasons for late diagnosis. Most common complaints are flank pain (up to 80%) and/or dysuria (up to 54%). If the urinary tract is involved, then renal colic (24%) and gross hematuria (up to 20%) may occur. Prostate TB manifests itself by perineal pain and dysuria and in half of the cases by hematospermia. TB epididymo-orchitis always starts from epididymitis; 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. Nevertheless, in 32–40% of patients, the disease has a chronic or asymptomatic course [3, 16–20].

11.4.2 Physical Examination

Special attention should be paid to any fistula. Scrotal and perineal fistulae are highly suspicious for TB [18]. In the acute course of TB epididymitis, a hard, painful, enlarged epididymis intimately welded with the testis can be palpated. In

chronic cases 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 moderately enlarged tuberous prostate with weak pain [4, 5, 20].

11.4.3 Laboratory Tests

All patients with UGTB should be screened for pulmonary involvement and HIV infection.

11.4.3.1 Urinalysis and Culture Tests

Leukocyturia is found in 90–100% of patients with KTB and hematuria in 50–60% [3]. Before the "antibiotic era," sterile pyuria was a specific sign of KTB, but now up to 75% of patients have non-specific pyelonephritis alongside with KTB and therefore uropathogens and Mtb may be found in urine together [17–20]. The diagnosis of UGTB is absolutely confirmed when Mtb is detected, but in recent years Mtb could be found only in half of TB patients. Therefore, in patients suspected of having UGTB, but without documented evidence of Mtb, the diagnosis of urogenital TB has to be made on the basis of other features, such as skin test, histological findings, caverns revealed by intravenous pyelography, sterile pyuria, etc. [3, 21].

A microbiological confirmation of the diagnosis of UGTB may be made by culturing of *Mtb* (from an appropriate clinical sample such as urine, pus, semen, or tissue biopsy) or by identification of *Mtb* DNA using the rapid molecular diagnostic test, the GeneXpert® MTB/RIF assay. Due to the slow growth rate, conventional solid culture systems including Löwenstein-Jensen slant or Middlebrook 7H11 agar plates always require 8 weeks of incubation before a negative result can be reported. Unfortunately, today standard culture on standard media has low efficiency for UGTB patients. One of main reasons for false-negative results is nonoptimal empiric therapy for UTI, when a patient with UGTB masked by non-specific UTI is treated with amikacin and fluoroquinolones. Both these drugs negatively influence on a growth of Mtb.

What modern technologies of rapid MTB identification are available? First of all molecular genetic methods in TB diagnosis, which include:

- Detection of Mtb with different polymerase chain reaction (PCR) techniques (flash, real-time, Hain Lifescience)
- Determination of drug resistance of the pathogen (I–II line anti-TB drugs)
- Identification of type, strain of pathogen, and genotype determination of mycobacteria isolated from a patient (*M. tuberculosis*, non-tuberculous mycobacteria)

Also BACTEC MGIT 960 system, a fully automated and nonradiometric culture system, has been recommended for faster mycobacterial isolation from clinical specimens. The culture is monitored with the oxygen-quenching fluorescent sensor technology every 60 minutes, which provides a satisfactory performance in a short laboratory turnaround time when compared with conventional methods. The BACTEC MGIT 960 is therefore widely considered as the gold standard for the diagnosis of TB. But even this modern method may give false-negative results. Growth of Mtb in BACTEC MGIT 960 can go undetected, especially the most aggressive Beijing strain [3, 21].

11.4.3.2 Histology

Histological investigation of biopsy or surgical material may reveal epithelioid granuloma and caseous necrosis, both of which are soon replaced by fibrous tissue especially after suboptimal previous therapy. Prostate biopsy should only be performed after urethrography in order to exclude caverns [22, 23].

Fine-needle aspiration cytology (FNAC) may be useful to diagnose TB of the external male genitals [4]. 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 non-treated patients with active UGTB.

11.4.3.3 Imaging

Ultrasonography Ultrasound investigation may give indirect evidence of urogenital TB only. As prostate TB is accompanied by KTB in 79% of cases [24], pathological findings detected by renal ultrasound in patients with "chronic prostatitis" are very suspicious for urogenital TB. TB epididymitis and orchitis present as diffusely enlarged lesions, which may be homogeneous or heterogeneous and can also occur as nodular enlarged heterogeneously hypoechoic lesions [24]. Transrectal ultrasound may reveal hypo- and hyperechoic lesions of the prostate, predominantly in the peripheral zone, but also as prostatolithiasis which may be calcified zones of TB inflammation [24].

Radiological examinations are not useful for diagnosis of UGTB in early stages. Intravenous pyelography (IVP) is indicated for patients with leukocyturia and/or abnormalities on ultrasound investigations. Retrograde urethrography should be performed in all patients with GTB to exclude caverns in the prostate. Multi-sliced computer tomography (CT) is more informative. On 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 [25, 26].

Endoscopy Generally, instrumental interventions are of limited value for the diagnostic work-up in UGTB. However, cystoscopy is indicated in all UGTB patients with dysuria. 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 [3].

11.5 Treatment

11.5.1 Chemotherapy

As UGTB is a contagious disease, anti-TB therapy should start as soon as possible. Once a diagnosis of active TB is made, TB drug treatment should follow WHO and specialist society guidelines [27–31].

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, or in case of recurrence of the disease, second or third line of anti-TB drugs are indicated [32].

11.5.2 Most Common Adverse Effects of Anti-TB Therapy

Long-term exposure to anti-tuberculosis medication increases the risk of adverse drug reactions and toxicity. The liver is vulnerable to injury from the first-line anti-tuberculosis drugs [33]. Anti-tuberculosis (anti-TB) drug-induced hepatotoxicity is the most common side effect leading to interruption of therapy. This may result in mortality, long-term morbidity, and reduced compliance to therapy. Older age and poor nutritional status including baseline hypoalbuminemia were independent predictors of development of anti-TB hepatitis [34]. In another study old age, anemia, MDR-TB medication, overweight/obesity status, and smoking history were independent risk factors for anti-tuberculosis adverse drug reactions [35].

Linezolid is one of the few drugs that have shown promise in treating extensively drug-resistant (XDR) tuberculosis and multidrug-resistant (MDR) tuberculosis. Long-term linezolid use is associated with toxicities such as peripheral and optic neuropathies. Diabetes mellitus, especially when uncontrolled, can also result in peripheral neuropathy if a patient receives linezolid [35].

11.5.3 Negative Influence of Tuberculosis and Anti-TB Therapy on Sexual Function

Not only genital forms of TB might have negative influence on female reproductive function. Pulmonary TB is accompanied by menstrual abnormalities in 66% of women. However, after completing anti-tuberculosis treatment, 76% of women with menstrual abnormalities resumed normal menstrual cycles [36, 37].

Anti-TB treatment has a negative effect on the ejaculate: a 2-month course of anti-TB therapy resulted in a decrease of sperm quality by 23.9% and decreased number of actively motile sperm by 10.6% and the number of morphologically normal sperm by 32.3% [38]. To evaluate sexual function, 98 pulmonary TB male patients were enrolled in retrospective study. The intravaginal latency time was estimated before the start of anti-TB therapy and in 3 months of anti-TB therapy. On baseline 14.3% of pulmonary TB patients had ejaculatory disorders, 10.2% had premature ejaculation, and 4.1% had delayed ejaculation. The remaining 85.7% of patients had normal ejaculation [39, 40]. After 3 months of the therapy with four anti-TB drugs (isoniazid, rifampicin, pyrazinamide, and streptomycin), the spectrum of sexual dysfunction changed significantly. The share of patients with normal ejaculation decreased to 61.2%, and the frequency of premature ejaculation doubled (20.4%), and delayed ejaculation was diagnosed 4.5 times more often (18.4%) [40].

Authors emphasized that the proportion of ejaculatory disorders in male patients with pulmonary TB initially was the same as in the general population. They concluded that tuberculosis as a disease doesn't influence the ejaculatory function. But anti-TB therapy with four drugs during 3 months significantly worsened the ejaculatory function for every fourth patient. Authors explained a quadruple increase of frequency of delayed ejaculation by neurotoxicity of some of the anti-TB drugs. So, tuberculosis as a disease doesn't damage the ejaculatory function, but anti-TB therapy does. Future research should look for ways to prevent this complication [40].

In Russia and especially in Siberia, there is currently an epidemic of TB [41]. About two-thirds of newly diagnosed patients are young men, and sexual function and fertility is very important for them. The sexual function was studied in 105 newly diagnosed patients with pulmonary tuberculosis aged 18–39 years [40]. Although no diseases of urogenital system could be found, patients with pulmonary TB showed deterioration of several parameters from sexual desire to orgasm. Patients with widespread cavernous pulmonary TB had higher level of sexual dysfunction than patients with smaller forms of pulmonary TB, and this level had strong correlation with the severity of the sexual dysfunction.

Complex anti-TB chemotherapy improved the fertility of pulmonary TB patients, most likely by arresting the systematic inflammation and reducing intoxication, but even after 6 months of treatment, they had significantly decreased scores on sexual function tests by valid questionnaires [60].

11.5.4 Surgery

Surgical intervention is indicated in advanced cases and for correction of complications. The most relevant surgical interventions are presented in Table 11.1.

All surgical interventions should be performed under coverage of anti-TB therapy. The treatment duration is decided after histological investigation of the removed tissue [42–44].

11.6 Conclusion

Tuberculosis still now is the most important cause of death from an infectious disease in adult worldwide. Urogenital tuberculosis is often missed clinically due to its insidious onset, chronic non-specific symptoms and cryptic and protean clinical manifestations, and lack of clinical awareness. Delays in making a diagnosis result in disease progression, tissue and organ damage, and renal failure. UGTB can present with chronic urinary tract inflammation, hematuria, obstructive uropathy, infertility, and renal or testicular mass and can contribute to the development of urothelial cancer; sterile pyuria today is not typical for UGTB.

Table 11.1 Surgical treatment of urogenital TB

Indication	Surgery
1. Kidney TB	
KTB-3, resistant to standard therapy (notable cavern with pyogenic layer remains, Mtb in urine, pyuria) for 2–4 months	Cavernectomy (partial nephrectomy), optimal – laparoscopically
KTB-4	Nephrectomy, optimal – laparoscopically
2. Urinary tract tuberculosis	
Stricture of ureter, urethra	Standard plastic operation
Bladder TB stage 4	Cystectomy (in male patients – cystoprostatectomy) followed by conduit or bladder replacement
3. TB epididymo-orchitis	
Fluctuation, abscess	Incision of abscess and drainage
Torpid course with low efficiency of conservative treatment for 1–2 months	Epididymo-orchiectomy
4. Prostate TB (normally prostate TB is not indicated for surgery)	
Development of abscess	Drainage of abscess

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