

EAU Guidelines

EAU Guidelines for the Management of Genitourinary Tuberculosis

Mete Çek*, Severin Lenk, Kurt G. Naber, Michael C. Bishop, Truls E. Bjerklund Johansen, Henry Botto, Magnus Grabe, Bernard Lobel, Juan Palou Redorta, Peter Tenke

the Members of the Urinary Tract Infection (UTI) Working Group of the European Association of Urology (EAU) Guidelines Office

Department of Urology, Taksim Teaching Hospital, Istanbul, Turkey

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Abstract

Nearly one third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. Moreover, tuberculosis is the most common opportunistic infection in AIDS patients. Genitourinary tuberculosis is not very common but it is considered as a severe form of extra-pulmonary tuberculosis

The diagnosis of genitourinary tuberculosis is made based on culture studies by isolation of the causative organism; however, biopsy material on conventional solid media may occasionally be required.

Drug treatment is the first line therapy in genitourinary tuberculosis. Treatment regimens of 6 months are effective in most of the patients. Although chemotherapy is the mainstay of treatment, surgery in the form of ablation or reconstruction may be unavoidable. Both radical and reconstructive surgery should be carried out in the first 2 months of intensive chemotherapy.

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1. History and background

For 7000 years tuberculosis (TB) have been observed and in 1882 Koch described the pathogenesis of the disease. His postulates became the basis for the study of all infectious diseases. In 1937, Wildbolz stressed that renal and epididymal TB were local manifestations of the same blood-borne infection. Wildbolz was the first person to use the term genitourinary tuberculosis (GUTB).

The World Health Organization (WHO) estimates that nearly one third of the world's population is infected with *Mycobacterium tuberculosis* and there

are 8 to 10 million new active cases of TB each year, and about two million die [1].

More than 90% of the global TB cases and deaths occur in the developing world. Seventy five (75)% of these patients are in the most economically productive age group [1].

Multidrug resistance, which is caused by poorly managed TB treatment, is a growing problem of serious concern in many countries around the world [1].

Globally, TB is the most common opportunistic infection in AIDS patients and HIV infection is a cofactor with one of the highest risk ratios for the development of TB in people already infected with *M. tuberculosis*. However, extra-pulmonary TB is still present, particularly in the suburbs of big cities, independent of HIV [2].

* Corresponding author. Tel. +90 532 262 6032;
Fax: +90 212 233 9804/234 5139.
E-mail address: cekmd@doruk.net.tr (M. Çek).

Although uncommon, GUTB is considered as a severe form of extra-pulmonary tuberculosis [1]. While renal TB is uncommon in developed countries, as many as 15% to 20% of TB patients in developing countries are found with *M. tuberculosis* in the urine [3]. Genitourinary tuberculosis remains one of the most common forms of secondary or extra-pulmonary disease. Genitourinary tuberculosis (GUTB) has been inconsistently reported to account for 20% to 73% of all cases of extra-pulmonary tuberculosis in the general population but is much rarer in children [4].

Nevertheless, reports of GUTB are relatively rare and are mainly published as case reports or as retrospective clinical reviews.

Properly applied TB chemotherapy is effective in curing the chain of transmission. The best prevention of TB is therefore the cure of infectious TB cases. In this regard, the directly observed treatment (DOTS) strategy is recognized as one of the most cost-effective health interventions [1].

2. Epidemiology

The WHO estimated that there were 484.000 new TB cases in Europe in 2001, representing 6% of the global TB burden. The Russian Federation had the ninth highest burden of TB in the world. Within Europe, the TB incidence varies enormously, from five per 100.000 population in Sweden to 181 per 100.000 population in Kazakhstan [1].

The female/male ratio was 0.4 among new pulmonary TB cases with a positive sputum smear. This may require research on sex inequality in accessing TB services in some settings [1]. High rates of TB are associated with socioeconomic crisis, weaknesses in health systems, epidemics of HIV and multidrug-resistant TB, and poor interventions to control TB among vulnerable populations. Recent analysis shows that 2.6% of all new TB cases in Europe in 2000 were attributable to HIV co-infection. In the Russian Federation, 1% of all new cases of TB were estimated to be HIV-positive and 35% of the adults with AIDS have died from TB [1].

The incidence of extra-pulmonary tuberculosis is higher in dialysis patients than in the general population [5]. GUTB is rare among people under the age of twenty five, and these patients are more likely to have a family history positive for TB [6].

Mycobacterial infection, mainly by *M. tuberculosis*, has an important impact on kidney transplant recipients, particularly during the first year after surgery [7].

3. Pathogenesis

Almost all *M. tuberculosis* infections are acquired by the inhalation of aerosolized droplet nuclei (1 to 5 μm), which reach the pulmonary alveoli. The probability that a person will become infected depends on the duration of exposure to the source case, the size of the bacillary inoculum inhaled, and the infectivity of the mycobacterial strain. The probability of a competent host's developing active TB after *M. tuberculosis* infection is 5% to 10% over the person's lifetime. Up to 50% of the active disease occurs within 2 years of infection [3].

Tuberculosis of the kidney, the urinary tract, and the male genital tract like other forms of tuberculosis (pulmonary, non-pulmonary), is caused by members of the *Mycobacterium* (*M.*) *tuberculosis* complex [3].

The development of disease depends on the interaction between the pathogen and the immune response of the host. Although the organism evokes both a humoral and a cellular immune response, cellular immune response determines the outcome of an infection.

During the initial primary pulmonary infection, the *M. tuberculosis* organisms multiply and evoke an inflammatory reaction. As there is still little host defence to the multiplication of the bacteria at this stage, rapid spread occurs, by way of the lymphatics and the blood stream. Within about 4 weeks, however, the rate of multiplication decreases as the host response develops and the dissemination ceases [3].

Genitourinary TB is usually caused by metastatic spread of organisms through the blood stream during the initial infection. Active disease results from the reactivation of the initial infection [3].

4. Microbiology

By far the most common causative organism is the human tubercle bacillus. Tuberculosis caused by the bovine tubercle bacillus *M. bovis* is now uncommon in industrially developed nations. Therefore, genitourinary TB is synonymous with disease due to *M. tuberculosis*, which is a strictly aerobic but slowly growing microorganism, with a doubling time of 15 to 20 hours. Acid-fast bacillus smear is the most reliable test, with a sensitivity of 22% to 81% [3]. Non-tuberculous mycobacteria rarely cause disease in the genitourinary system.

Molecular methods, including nucleic acid hybridization and polymerase chain reaction of either DNA or a rRNA, have been developed but are relatively insen-

sitive in clinical specimens, unless large numbers of organisms are present [8–12].

As non-tuberculous mycobacteria may frequently be resistant to first-line drugs, early sensitivity tests must include a complete spectrum of drug sensitivities [3].

5. Pathology

5.1. Kidney

Tuberculosis may involve the kidney as part of generalized disseminated infection or as localized genitourinary disease. The kidney is usually infected by hematogenous spread of bacilli from a focus of infection in the lungs and/or bowel. Mostly, GUTB is a reactivation of the tuberculosis from a period of dormancy. Clinically, renal tuberculosis usually presents unilaterally, but post mortem studies showed that the disease frequently was bilateral.

The healing process results in fibrous tissue and calcium salts being deposited, producing the classic calcified lesion. The occurrence of renal calcification is common in TB and may require surgical excision [3]. In the management of this complication, the aim should be to retain as much functioning renal tissue as possible. This monitoring should continue for 10 years or longer, because a sudden increase in size may occur that requires surgical intervention [13,14]. Hypertension may occur as a complication of severe unilateral TB and reduced renal blood flow, and two thirds of patients with extensive unilateral tuberculous nephropathy achieve a substantial fall in blood pressure after nephrectomy [15].

5.2. Ureter

Tuberculous ureteritis is always an extension of the disease from the kidney.

The site most commonly affected is the ureterovesical junction. This is invariably secondary to extensive disease of the kidney and, if not recognized early, can rapidly cause complete destruction.

Very occasionally, the whole of the ureter is involved. In such patients, the kidney shows extensive disease, is often nonfunctioning, and is calcified [3].

5.3. Bladder

Bladder lesions are without exception secondary to renal TB. The earliest forms of infection start around one or another ureteral orifice. If the disease continues to progress, the inflammation and the fibrosis which eventually follows contracts and can either produce a stricture or become withdrawn, rigid, and dilated, assuming the classic golf-hole appearance [3].

5.4. Testis

Testicular involvement is less common than tuberculous epididymitis, and is usually a result of direct invasive epididymitis.

Tuberculous orchitis with no epididymal involvement is a very rare presentation. It is impossible to differentiate such a swelling from a tumor, and early exploration is therefore required if a rapid response to antituberculous chemotherapy does not occur [16,17].

5.5. Epididymis

Genital tuberculosis in males most commonly involves the epididymis followed by the prostate. Tuberculous epididymitis probably is a result of blood-borne infection because it often is an isolated finding without urinary tract involvement. It is important to be aware that a high proportion (50–75%) of men with genital tuberculosis have radiologic abnormalities in the urinary tract. The urinary tract of all such patients with primary location of tuberculous infection on the epididymis should be investigated [8].

Tuberculous foci in the epididymis are caused by metastatic spread of organisms through the blood stream. The disease usually starts in the globus minor, because it has a greater blood supply than other parts of the epididymis. Tuberculous epididymitis may be the first and only presenting symptom of genitourinary TB [3].

The disease usually develops in young, sexually active males, and in 70% of patients, there is a previous history of TB. The usual presentation is a painful, inflamed scrotal swelling. The globus minor alone is affected in 40% of cases. The management of tuberculous epididymitis may pose problems if *M. tuberculosis* cannot be isolated from the urine. In the acute phase, the inflammatory reaction involves the testis, so it is difficult to differentiate the lesion from acute epididymo-orchitis.

If there is no sinus and the *M. tuberculosis* organisms are absent from the urine, treatment with an appropriate antibiotic may be started. In the absence of any improvement, within 2 to 3 weeks, antituberculous chemotherapy should be started. After an additional 3 weeks, if the lesion becomes nodular, firm, and painless, exploration of the testis is mandatory without delay [3].

The transmission of genital TB from male to female is very rare. Occasional reports of pelvic tuberculosis in the sexual partner of patients with tuberculous epididymo-orchitis suggest the possibility of female-to-male venereal transmission [18].

Embryo quality and pregnancy outcome in sperm retrieval and ICSI seem to be comparable in both the

tuberculous and the nontuberculous obstructive azoospermia patients. Previous tuberculous epididymitis in patients with obstructive azoospermia does not seem to affect the outcome of sperm retrieval and ICSI. The outcome of sperm retrieval followed by intracytoplasmic sperm injection is not affected [19].

5.6. Prostate

TB of the prostate is rare, and in many cases, it is diagnosed by the pathologist or is found incidentally after a transurethral resection. The route of infection is through the hematogenous spread of organisms. Tuberculous prostatitis results from antegrade infection within the urinary tract [3].

5.7. Penis

TB of the penis is very rare. Primary TB of the penis occurs after coital contact with organisms already present in the female genital tract or by contamination from infected clothing [20]. The diagnosis is confirmed by biopsy; these lesions generally rapidly respond to antituberculous chemotherapy [3]. Endometrial tuberculosis in the partner of a patient who had primary culture positive *Mycobacterium tuberculosis* infection of the penis has been reported. These organisms were confirmed to be indistinguishable by use of molecular techniques [21].

5.8. Urethra

TB of the urethra is very rare [3,22]. The patients should receive chemotherapy as initial treatment [3].

6. Diagnosis

The diagnosis of GUTB is difficult because its symptoms are non-specific. The most important step in diagnosing GUTB is patient history. The knowledge of tuberculosis infection early in life either as primary pulmonary manifestation or as an extra-pulmonary manifestation gives an important clue in a large number of cases. One has to be aware that the latency between pulmonary manifestation and GUTB is enormous. In some cases, it could take more than 30 years before GUTB becomes evident [8].

Especially in urinary tuberculosis, voiding problems and chronic urgency non-responding to antibacterial drug regimens, are indicative of GUTB. In men, chronic epididymitis is the typical manifestation of tuberculosis of the male genital tract, mostly combined with scrotal fistulas.

Other symptoms that sometimes occur include back, flank, and suprapubic pain, hematuria, frequency, and

nocturia. Renal colic is uncommon, occurring in fewer than 10% of patients, and constitutional symptoms such as fever, weight loss, and night sweats are unusual. Commonly, the symptoms are intermittent and have been present for some time before the patient seeks medical advice [8].

A microbiologic diagnosis of tuberculosis is usually made by isolation of the causative organism from urine or biopsy material on conventional solid media or by an automated system such as radiometry.

A positive culture or histological analysis of biopsy specimens possibly combined with PCR is still required in most patients for a definite diagnosis. In 25–30% the diagnosis of GUTB is established on the basis of the histological pattern and/or by detection of the *Mycobacterium tuberculosis* complex by PCR [8].

Detection of acid-fast bacilli from urine samples by microscopy (Ziehl-Neelsen acid fast stain) is not reliable, because of the possible presence of *M. smegmatis*, which are acid-fast bacilli too. The biological activity of tuberculosis can only be assessed by cultivating mycobacteria.

Bacillary load, extent of disease and anatomical site are considerations in determining the disease severity and therefore the appropriate treatment. Genitourinary TB, together with some other forms of EPTB is classified as severe TB [1].

GUTB is a form of secondary tuberculosis with vague symptoms. Therefore, urologists should always consider the diagnosis of genitourinary TB in a patient presenting with vague, long-standing urinary symptoms for which there are no obvious cause. There is often a latent period of 20 years or more between infection with the tubercle bacillus and the expression of genitourinary tuberculosis [23].

The most common laboratory abnormalities are pyuria, albuminuria, and hematuria. Seventy five (75)% of patients has an abnormal chest roentgenogram on admission. Eighty eight (88)% of patients tested have positive skin tests and 63% tested have abnormal excretory urography. Sixteen (16)% show renal calcification [23]. Renal tuberculosis is accompanied by manifestations of the urinary syndrome in 70.4% of cases and by the presence of *Mycobacteria tuberculosis* in 100% [24].

Genitourinary TB is very uncommon in children because the symptoms of renal TB do not appear for 3 to 10 or more years after the primary infection [3].

The patient usually complains of frequent painless micturition, at first only at night but later during the day as well. Urgency is uncommon unless there is extensive bladder involvement. The urine is normally sterile, and, in a high proportion of patients, it contains leukocytes.

However, up to 20% of patients may not have any leukocytes in the urine [3].

Overt hematuria is present in only 10% of patients, but microscopic hematuria is present in up to 50%. Renal and suprapubic pain is a rare presenting symptom and usually means extensive involvement of the kidney and bladder. Suprapubic pain is always accompanied by very frequent micturition.

Although hematospermia is a rare presenting symptom, TB should always be considered in patients who are seen with repeated attacks of hematospermia as the only presenting symptom, even if there is no other evidence of genitourinary TB [3]. Recurrent cystitis is also a warning sign. It may be necessary to repeat the investigations, because *M. tuberculosis* may be difficult to isolate from the urine. The only presenting symptom may be a painful testicular swelling. Early morning specimens of urine should be examined if it is difficult to differentiate between TB and nonspecific epididymo-orchitis [3]. Rarely, the diagnosis is an incidental finding that is made after transurethral resection of the prostate when the pathologist reports foci of TB. These patients should be given antituberculous chemotherapy (Level 4).

6.1. Tuberculin test

The tuberculin test is accomplished by intradermal injection of a purified protein derivative of tuberculin. An inflammatory reaction develops at the site and reaches a maximum between 48 and 72 hours after injection. This reaction consists of a central indurated zone surrounded by an area of erythema; it is assessed by measuring the diameter of the indurated area. A person's ability to respond to the local concentration of the injection may be decreased by malignancy, nutritional deficiencies, steroid therapy, irradiation, and AIDS [3].

The CDC has recommended three cut points for defining a positive tuberculin reaction: induration of 5 mm or greater, 10 mm or greater, and 15 mm or greater. The individuals that apply to each of these cut points are identified in Table 1 [25].

A positive skin test supports the diagnosis of tuberculosis, but a negative skin test does not necessarily exclude an extra-pulmonary manifestation. This is especially true in cases of GUTB [8].

6.2. Urine examination

The urine is examined for red blood cells and leukocytes, and the pH and concentration are noted. The urine is also cultured for other potential uropathogens since secondary bacterial infections may be detected in about 20% of cases. "Sterile pyuria" is

Table 1

Criteria for tuberculin positivity, by risk group

| |
|---|
| Reaction ≥ 5 mm of Induration |
| HIV positive persons |
| Recent contacts of tuberculosis case patients |
| Fibrotic changes on chest radiograph consistent with prior TB |
| Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/day of prednisone for 1 mo or more) |
| Reaction ≥ 10 mm of induration |
| Recent immigrants from high-prevalence counties |
| Injection drug abusers |
| Residents and employees of high risk congregate settings |
| Mycobacterial laboratory personnel |
| Persons with the following clinical conditions that place them at high risk: Silicosis, diabetes mellitus, chronic renal failure, some hematological disorders, specific malignancies, weight loss of ≥ 10 of ideal body weight, gastrectomy, and jejunoileal bypass |
| Children younger than 4 yr. or infants, children and adolescents exposed to adults at high risk |
| Reaction ≥ 15 mm of induration; Patients with no risk factors for TB. |

the classic urinary finding on routine urinalysis and culture [8].

The diagnosis of genitourinary tuberculosis is made based on culture studies. At least three, but preferably five, consecutive early morning specimens of urine should be cultured, each onto two slants: [1] a plain Löwenstein-Jensen culture medium to isolate *M. tuberculosis*, bacille Calmette-Guérin (BCG), and the occasional nontuberculous mycobacteria; and [2] a pyruvic egg medium containing penicillin to identify *M. bovis*, which is partially anaerobic and grows below the surface of the culture medium. Each specimen of urine should be inoculated as soon as possible after collection [3]. In recent years, nucleic-acid amplification techniques, such as polymerase chain reaction (PCR), have been investigated extensively for the detection of *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. microti*, *M. africanum*) and other mycobacteria in clinical specimens, notably sputum. Relatively few studies have specifically evaluated PCR for detection of genitourinary tuberculosis, and these show the technique to be sensitive and specific, although some urine specimens contain inhibitory substances. In addition, PCR has been used to detect mycobacterial DNA in urine in cases of HIV-related disseminated tuberculosis [8].

A positive culture or histological analysis of biopsy specimens possibly combined with PCR is still required in most patients for a definite diagnosis. In 25–30%, the diagnosis of GUTB is established based on the histological pattern and/or by detection of the *Mycobacterium tuberculosis* complex by PCR.

Detection of acid-fast bacilli from urine samples by microscopy (Ziehl-Neelsen acid fast stain) is not reliable, because of the possible presence of *M. smegmatis*, which are acid-fast bacilli too. However, the biological activity of tuberculosis can only be assessed by cultivating mycobacteria [8].

6.3. Radiography

6.3.1. Plain radiographs

Plain X-ray films of the urinary tract are important because they may show calcification in the renal areas and in the lower genitourinary tract. Renal calcification may not represent inactive process, which requires further evaluation [3,26].

6.3.2. Intravenous urography

Radiological imaging can be helpful to detect GUTB. Characteristic signs on intravenous pyelogram and computed tomography are useful in depicting GUTB. Radiologically detectable manifestations of tuberculosis allow earlier diagnosis and the timely initiation of appropriate therapy, thus reducing patient morbidity [8].

In the early course of disease, it is often possible on intravenous urography to detect changes in a single calyx with evidence of parenchymal necrosis. The renal lesion may appear as a distortion of a calyx, as a calyx that is fibrosed and completely occluded (lost calyx from infundibular stenosis), as multiple small calyceal deformities, or as severe calyceal and parenchymal destruction. In more advanced disease, urography will show calyceal distortion, ureteric strictures, and bladder fibrosis [8].

The introduction of the high-dose intravenous urogram is now accepted as standard practice. A dynamic study of the diseased ureter can be performed by utilizing image-intensified endoscopy. This functional information about ureteral peristalsis provides further information about the extent of the disease, the peristaltic activity, the amount of fibrosis that is present, and the length of a stricture, particularly at the ureterovesical junction. A nonfunctioning or extensively diseased kidney indicates irreversible tuberculous disease [3].

6.3.3. Retrograde pyelography

Retrograde pyelography is now rarely necessary, but there are two indications for its use:

- (1) a stricture at the lower end of the ureter, when it is necessary to try to delineate the length of the stricture and the amount of obstruction and dilatation above the stricture.

- (2) ureteral catheterization, which may be required to obtain urine samples for culture from each kidney [3].

6.3.4. Ultrasonography and CT

Ultrasound examination of the urinary tract may reveal renal calyceal dilation and more overt evidence of obstruction. Computed tomography (CT) and nuclear magnetic imaging are important for differential diagnosis (renal parenchymal masses, scarring, auto-nephrectomy) [8].

6.4. Cystoscopy and ureteroscopy

Endoscopy must always be performed with the patient under general anesthesia with a muscle relaxant to reduce the risk of hemorrhage. The phase of bladder filling should be performed under direct vision. Indications for ureteroscopy are rare [3]. Renal tuberculosis should be included in the differential diagnosis of lateralizing hematuria, especially in the absence of an obvious cause for the bleeding. Direct culture of urine from the renal pelvis may have more sensitivity than culture of voided urine in this circumstance [27].

6.4.1. Bladder biopsy

Bladder biopsy is contraindicated in the presence of acute tuberculous cystitis. It is acceptable only in patients with tubercles or with ulcers some distance from a normal ureteral orifice, because a diagnosis of carcinoma must be excluded if such lesions are seen [3].

The diagnostic algorithm recommended in cases suspected for GUTB is shown in Table 2.

7. Medical treatment

Modern short-course anti-tuberculous drug regimens are effective in all forms of tuberculosis.

Table 2

Diagnostic procedure of GUTB

| |
|---|
| Suspected diagnosis |
| Case history (earlier pulmonary or extra-pulmonary tuberculosis) |
| Symptoms |
| Physical examination |
| Skin test |
| Urine analysis (leucocytes, erythrocytes, bacteria) |
| Radiological imaging |
| <input type="checkbox"/> intravenous pyelogram |
| <input type="checkbox"/> CT |
| Definitive Diagnosis |
| Microscopic examination (Ziehl-Neelsen acid fast stain) |
| Yellow egg cultures (urine, smear, secretion, ejaculate, tissue samples) |
| PCR |
| Histological examination (tissue samples) |
| <input type="checkbox"/> combined with Ziehl-Neelsen acid-fast stain and/or PCR |

According to the World Health Organization the anti-tuberculous drug treatment is based on an initial 2-month intensive phase of treatment with three or four drugs daily rifampicin, isoniazid, pyrazinamide, and ethambutol (or streptomycin) to destroy almost all tubercle bacilli. This is followed by a 4-month continuation phase with only two drugs mostly rifampicin and isoniazid. In the continuation phase the drug may be given twice or thrice weekly.

In addition, in GUTB drug treatment is the first line therapy. In the course of a follow-up of more than 40 years, the treatment time was reduced from 24 months to 6 months. Only in complicated cases (recurrences of tuberculosis, immunosuppression and HIV/Aids) a 9 to 12 month therapy is necessary.

A serious problem at present is the high percentage of primary drug resistance in patients with tuberculosis. Risk factors for multidrug-resistance (MDR) TB include prior treatment and residence in countries with known high MDR TB rates. In a study from the Russian Research Institute of Phthisiopulmology, 50 isolates of *M. tuberculosis* obtained from patients referred from various parts of Russia were analysed by PCR and sequenced to study the mechanism of rifampicin resistance. Drug resistance was detected in 33 patients out of the 50 from whom cultures were isolated. Most of the isolates were resistant to rifampicin ($n = 25$), isoniazid ($n = 14$), and streptomycin ($n = 7$). Multi-drug resistance was common. Only 6% of the isolates were resistant to one drug, whereas resistance to two, three, four, and five drugs was seen in 8, 14, 32, and 40%, respectively. Fully susceptible isolates were derived from only 17 patients. In rifampicin-resistant strains, a number of previously unrecognized genetic alterations (point mutations and deletions) were found in the *rpoB* locus. The *rpoB* locus is responsible for a high level of rifampicin resistance. ($>500 \mu\text{g/ml}$ in egg-based medium) [8].

In cases with MDR TB as defined by the WHO, i.e. caused by bacilli resistant to rifampicin and isoniazid, with or without resistance to other drugs, therapy requires the use of at least four drugs that are selected on the basis of a drug susceptibility test (ethionamide, prothionamide, quinolones, clarithromycin, cycloserin, kanamycin, viomycin, capreomycin, thiacetazone, and para-amino-salicylic acid). These drugs are less effective and often more toxic than the first line drugs.

The duration of therapy is based on the bacteriologic response but may be 18 months and longer.

Mycobacterium bovis harbours a primary resistance to pyrazinamide and is found in a high percentage of

patients with GUTB. In clinical practice, pyrazinamide should be avoided in those cases not only because of the likelihood of primary resistance but also because of the induction of hyperuricaemia, and hyperuricuria, which, might be detrimental in patients with GUTB.

Patients with GUTB caused by *M. tuberculosis* who are treated with pyrazinamide in the intensive treatment phase should get a xanthinoxidase-inhibitor in addition.

A 6-month short course of anti-tuberculous drug regimen is also effective in uncomplicated GUTB.

Special considerations apply to the treatment of tuberculosis in patients with impaired renal function. Rifampicin, isoniazid, pyrazinamide, prothionamide, and ethionamide may be given in normal dosage. They are eliminated in the bile or broken down to metabolites that are not excreted by the kidney. Care is required in the use of streptomycin, other aminoglycosides, and ethambutol. These are wholly excreted via kidney.

Ethambutol causes optic neuritis, which may be irreversible, and reduced dose should be given according to the glomerular filtration rate (GFR). Streptomycin and other aminoglycosides are ototoxic and nephrotoxic, and should not be given to patients with renal failure and especially after renal transplantation because cyclosporine involves also a high risk of nephrotoxicity. Encephalopathy is an uncommon complication of isoniazid and can be prevented by pyridoxine (25 to 50 mg per day).

Rifampicin increases the rate of metabolism of corticosteroids, cyclosporine, and lacrolimus.

Regular measurement of the concentration of cyclosporine and lacrolimus in the blood of such patients (mostly patients after transplantation) is recommended.

In HIV-patients, the antiretroviral therapy interacts adversely with rifampicin. When rifabutin is given instead of rifampicin the therapy must be extended to 9 to 12 months.

For GUTB the drug treatment recommendations were summarized (according to pulmonary tuberculosis) in Tables 3 and 4.

8. Surgical treatment

Although chemotherapy is the mainstay of treatment, ablative surgery as a first-line management may be unavoidable for sepsis or abscesses [28].

Surgical excision of non-functioning kidneys or extensive lesion in partly functioning kidneys is controversial. Nephrectomy is indicated by complications

Table 3

First line antituberculous drug therapy

| Antituberculous drug | Dose mg/kg BW | Body weight | Daily dose |
|-------------------------------|-----------------|-------------|------------------|
| Isoniazid (INH) | 5 | <50 kg | 300 mg |
| Rifampicin (RMP) | 10 | >50 kg | 450 mg 600 mg |
| Pyrazinamide (PZA) | 25–35 | <50 kg | 1.5 g |
| | | >50 kg | 2.0 g |
| | | >75 kg | 2.5 g |
| Streptomycin (SM) | 15–20 | <50 kg | 0.75 g |
| | | >50 kg | 1.0 g |
| Ethambutol (EMB) ^a | 25 ^b | | 2.0 0.8–2.0 g |
| Prothionamide (PTA) | 5–15 | | 0.5–1.0 g |

^a not for children younger than 10 years.^b after two months 20 mg.

such as severe upper urinary tract infection (UTI) with Gram negative or Grampositive bacteria and/or urinary stones, and hypertension.

Reconstructive surgery, mainly the repair of strictures at the lower end of the ureter, and bladder augmentation for a small fibrotic bladder, is frequently required. Both radical and reconstructive surgery should be carried out in the first 2 months of intensive chemotherapy [13].

The overall incidence of surgical management of genitourinary tuberculosis in the past 20 years was reported to be about 0.5% of urological surgical procedures [29].

Early ureteral stenting or PCN in patients with tuberculous ureteral strictures may increase the opportunity for later reconstructive surgery and decrease the likelihood of renal loss [30]. In all other situations, *patients should have at least 4 weeks of extensive chemotherapy before surgery* [3].

8.1. Nephrectomy

The indications for nephrectomy are:

- (1) a nonfunctioning kidney with or without calcification;

Table 4

6-month regimens for the treatment of uncomplicated GUTB

| Intensive phase | Continuation phase |
|--|--|
| 3 months INH, RMP, EMB (or SM) daily | 3 months INH, RMP twice or thrice per week |
| 2 months INH, RMP, PZA, EMB daily | 4 months INH, RMP twice or thrice per week |

- (2) extensive disease involving the whole kidney, together with hypertension and ureteropelvic junction (UPJ) obstruction; and
- (3) coexisting renal carcinoma.

Almost 90% of all nonfunctioning kidneys had been destroyed and require nephrectomy [3].

Short-course chemotherapy has altered the philosophy of surgical management of extensive disease of the genitourinary tract. However, despite sterile urine after chemotherapy 50% of histologic preparations of nephrectomy tissues still show active TB [31,32].

8.2. Partial nephrectomy

There are two indications:

- (1) the localized polar lesion containing calcification that has failed to respond after 6 weeks of intensive chemotherapy, and
- (2) an area of calcification that is slowly increasing in size and is threatening to gradually destroy the whole kidney. Partial nephrectomy is not justified in the absence of calcification [3].

8.3. Abscess drainage

Open surgical drainage of an abscess should not be attempted. The contents of an abscess should be aspirated in a minimally invasive manner [3].

8.4. Epididymectomy

There are two indications:

- (1) a caseating abscess that is not responding to chemotherapy, and
- (2) a firm swelling that has remained unchanged or has slowly increased in size despite the use of antibiotics and antituberculous chemotherapy.

Orchidectomy is seldom required. Ligation of the contralateral vas is not needed. Epididymectomy should be performed through a scrotal incision [3].

8.5. Ureteral strictures

The most common site for tuberculous stricture is the ureterovesical junction (UVJ); stricture may also occur at the UPJ and, rarely, in the middle third of the ureter. Ureteral strictures may develop in more than 50% of patients with renal involvement [33].

8.5.1. UPJ Strictures

Double J ureteral catheters may be used in all types of ureteral strictures for several purposes like stenting

after dilatation, maintaining adequate drainage during the healing process of either medical therapy or surgery, and to assess the efficacy of therapy.

Both the Anderson-Hynes technique and the Culp technique give satisfactory results for the repair of UPJ strictures [3,28].

8.5.2. *Strictures of the middle third of the ureter*

The Davis intubation ureterostomy technique or passage of a double-J stent from the bladder, if technically possible should be preferred for the treatment of the strictures of the middle third of the ureter. The silicone stent should be left in place for at least 6 weeks [3].

8.5.3. *Strictures of the lower end of the ureter*

Strictures of the lower end of the ureter, which can either be managed medically or by surgery, occur in approximately 9% of patients. If obstruction at the lower end of the ureter is present at the start of chemotherapy, careful observation is required. These strictures may result from edema, and they respond to chemotherapy. The patient should receive chemotherapy and should be monitored by intravenous urograms at weekly intervals. Corticosteroids can be added to chemotherapy if there is deterioration or no improvement after 3 weeks. If there is deterioration or no improvement after a 6-week period, surgical reimplantation is carried out if an initial attempt at dilatation has failed [3].

Double-J catheter drainage may be used during this period for assessing the efficacy of medical therapy.

8.5.4. *Ureteral dilatation*

Endoscopic dilatation has been referred to by some authors, but failure rates are high and the process requires anesthesia [34].

9. Conclusions with level of evidence and grade of recommendation

Genitourinary TB, together with some other forms of EPTB is classified as severe TB (Level 3). GUTB is a form of secondary tuberculosis with vague symptoms. Therefore, urologists should always consider the diagnosis of genitourinary TB in a patient presenting with vague, long-standing urinary symptoms for which there is no obvious cause (Level 4).

The diagnosis of genitourinary tuberculosis is made based on culture studies. At least three, but preferably five, consecutive early morning specimens of urine should be cultured.

In the early course of disease, it is often possible on intravenous urography to detect changes in a single calyx with evidence of parenchymal necrosis. The renal lesion may appear as a distortion of a calyx, as a calyx that is fibrosed and completely occluded (lost calyx from infundibular stenosis), as multiple small calyceal deformities, or as severe calyceal and parenchymal destruction. In more advanced disease, urography will show calyceal distortion, ureteric strictures, and bladder fibrosis (Level 4).

Medical treatment is the first line therapy in GUTB. The duration of medical therapy has been reduced to 6 months in uncomplicated cases. Only in complicated cases (recurrences of tuberculosis, immunosuppression and HIV/Aids) a 9 to 12 month therapy is necessary (Grade B).

Early ureteral stenting or percutaneous nephrostomy (PCN) in patients with tuberculous ureteral strictures may increase the opportunity for later reconstructive surgery and decrease the likelihood of renal loss (Level 2a). In all other situations, patients should have at least 4 weeks of extensive chemotherapy before surgery (Level 4).

Double J ureteral catheters may be used in all types of ureteral strictures for several purposes like stenting after dilatation, maintaining adequate drainage during the healing process of either medical therapy or surgery, and to assess the efficacy of therapy (Grade B).

Despite sterile urine after chemotherapy, 50% of histologic preparations of nephrectomy tissues show active TB (Level 3).

Nephrectomy may be recommended in those patients in whom hypertension is a complication of tuberculous nephropathy (Grade B)

A high proportion (50–75%) of men with genital tuberculosis have radiologic abnormalities in the urinary tract (Level 4). The urinary tract of all such patients with primary location of tuberculous infection on the epididymis should be investigated (Grade B).

Early exploration is suggested if a rapid response to antituberculous chemotherapy does not occur in cases of suspected tuberculous epididymitis and orchitis (Grade 3).

Previous tuberculous epididymitis in patients with obstructive azoospermia does not seem to affect the outcome of sperm retrieval and ICSI. The outcome of sperm retrieval followed by intracytoplasmic sperm injection is not affected (Level 3).

The diagnosis of tuberculous prostatitis may depend on an incidental finding that is made after transurethral resection of the prostate when the pathologist reports foci of TB (Level 3). These patients should be given antituberculous chemotherapy (Grade C).

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