# Extrapulmonary Tuberculosis of the Genitourinary System

Jennings Hernandez
Anjali Kumar

[1]**Abstract**

Tuberculosis, or TB, is an infectious bacterial disease caused by *Mycobacterium tuberculosis*, which most commonly affects the lungs. It is transmitted from person to person via droplets from the throat and lungs of the infected person to the uninfected. Its incidence appears to be increasing due to various factors, such as the spread of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). Once the infection has been established in the lungs it can then disseminate to multiple sites and organs of the body to cause a secondary infection. In this specific scenario the hematogenous dissemination carries the causative agents to the many components of the genitourinary system causing an infection in either they epididymis, testicles, prostate, urethra, kidney or bladder [1]. The onset and non‐specific symptoms of genitourinary tuberculosis (GUTB) often lead to delayed diagnosis and rapid progression to a non‐functioning kidney. However treatment is available in the course of antibiotics for six-months.

**Introduction**

*Mycobacterium* tuberculosis is present in approximately 30% of people worldwide in which genitourinary tuberculosis is the most common type after TB lymphadenitis and pleural effusion. It is found to affect women and men in a ratio of 2:1 respectively. Common age at presentation is 30-45 years. Recently, the frequency of TB increased among persons 45-55 years and in those older than 70 years.

Approximately 20% of patients who are affected with any pulmonary disease are also found to have genitourinary TB. Majority of these cases result in genitourinary organ damage and renal failure. Those populations residing in developing nations are more likely to exhibit these severe

[1] **Keywords**: Extrapulmonary TB, mycobacterium tuberculosis, HIV/AIDS, genitourinary system, secondary infection

consequences than those in already developed countries due to the greater availability in developed countries to the diagnose the condition at an earlier stage [2].

| | Incidence | | | Prevalence | | Mortality | |
|---|---|---|---|---|---|---|---|
| WHO region | N° in thousands | % of global total | Rate per 100000 pop | N° in thousands | %rate per 100 000 pop | N° in thousands | rate per 100 000 pop |
| Africa | 2828 | 30 | 351 | 3809 | 473 | 385 | 48 |
| The Americas | 282 | 3 | 31 | 221 | 24 | 29 | 3 |
| Eastern Mediterranean | 675 | 7 | 115 | 929 | 159 | 115 | 20 |
| Europe | 425 | 5 | 48 | 322 | 36 | 55 | 6 |
| South-East Asia | 3213 | 34 | 183 | 3805 | 216 | 477 | 27 |
| Western Pacific | 1946 | 21 | 109 | 2007 | 112 | 261 | 15 |
| Global | 9369 | 100 | 139 | 11093 | 164 | 1322 | 20 |

WHO/ **Tuberculosis** Fact sheet N°104 ; March 2010

TABLE 1: Estimated TB Incidence, Prevalence, Mortality

**Signs and Symptoms**

The extent of involvement within the GU-tract depends on the status of the patient's defense mechanism as well as the virulence of the organisms. Some of the most common signs of TB include; fever, fatigue, weakness, weight loss, and night sweats. Depending on the area affected by extra pulmonary TB, some of the nonspecific clinical features of GUTB include; hematuria, lower urinary tract symptoms, flank pain, scrotal swelling, polyuria, dysuria and acidic urinary pH with pyuria [3].

*Bladder TB*: Tuberculosis changes in the bladder occur via the ureteric orifice (UO), initially manifesting its presence as a localized superficial inflammation around a UO, followed by a granulomatous reaction with changes to produce the classical golf-hole appearance. Actual tubercles are rare in the bladder in the acute stage where they may have the appearance of grains of sand below a UO. In whole bladder involvement, there is presence of fibrous tissue that results

in the thickening of the bladder which decreases its capacity, becoming a non-compliant storage unit.

*Epididymal TB*: During an acute phase; unilateral enlargement of the scrotum resulting in testicular enlargement as a consequence of direct extension. Beading of the vasa may also occur.

*Prostatic TB*: Very uncommon. Acute urethritis is present due to the involvement of the urethral and periurethral glands that can involve the anterior urethra and lead to long inflammatory urethral strictures [3]. Urethral discharge may lead to involvement of the skin of the external genitalia, while seeding into the recipient's pelvic organs or GI-tract.

**Pathophysiology**

Tuberculosis of the genitourinary system is greatly due to the inhalation of aerosolized Mycobacterium Tuberculosis bacilli, which tends to duplicate in the alveolar macrophages and generally form a Ghon focus. Typically the mycobacteria remains contained in the granulomas of the lung or lymph nodes however, they can develop into the active disease form when an altered interaction between the pathogen and the immune cells occur [4]. When this occurs, the mycobacteria spreads to extrapulmonary organs by hematogenous dissemination and therefore can spread locally.

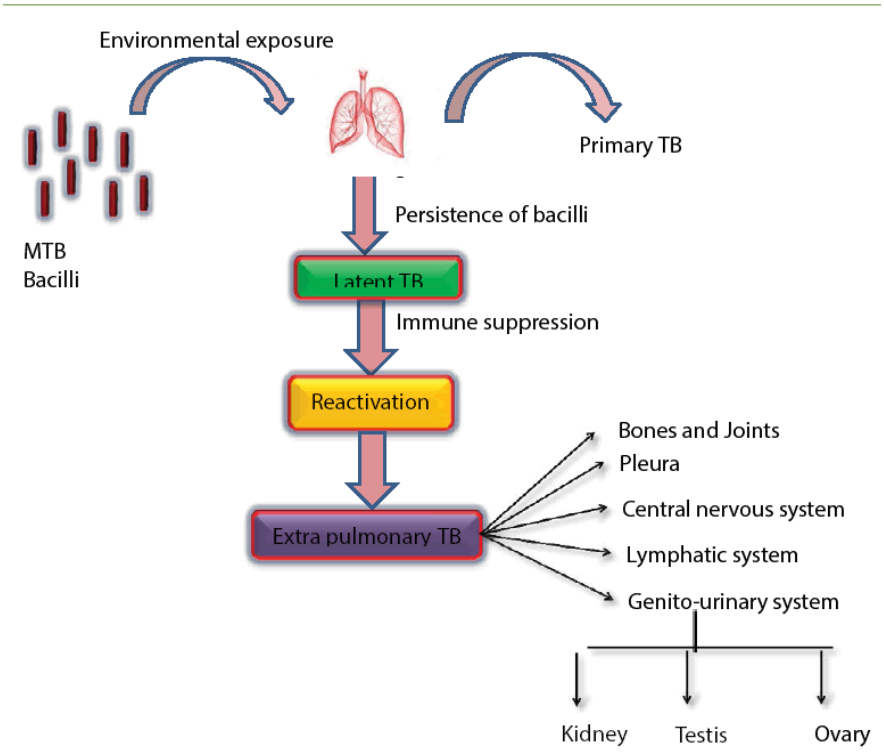


**Figure 1** Graphical representation of emergence of genital urinary tuberculosis.

FIGURE 1: Graphical representation of emergence of genital urinary tuberculosis [5].

Tuberculosis of the urinary tract takes on a descending route of infection as opposed to bacterial urinary infections. The TB bacilli travels to the kidneys by way of the bloodstream and as a result small renal cortical lesions develop. These small lesions can however heal spontaneously. Subsequently, the TB bacilli continues down the renal tubules ultimately affecting the calyces. Under those circumstances, necrosis and a papillary abscess may form, enlarge and expand towards the capsule of the kidney [5]. As a consequence, infected material can then infiltrate the renal pelvis by accumulation of the bacilli in the urine, spread antegrade and become embedded in the urothelium, ureter, bladder, and possibly adjacent genital tract. For this reason, there will be a narrowing or atresia ultimately causing distention or hydroureter and hydronephrosis. More so, GUTB is common and up to 10% of patients with renal TB will suffer

from bladder contractures. In addition, based on epidemiologic studies, known risk factors for reactivation of latent infection include but are not limited to: a reduction in serum 25-OH-vitamin D levels, HIV, malnutrition, tobacco smoke, indoor air pollution, alcoholism, silicosis, insulin dependent diabetes, renal failure, malignancy, and immunosuppressive treatments such as glucocorticoids [6].

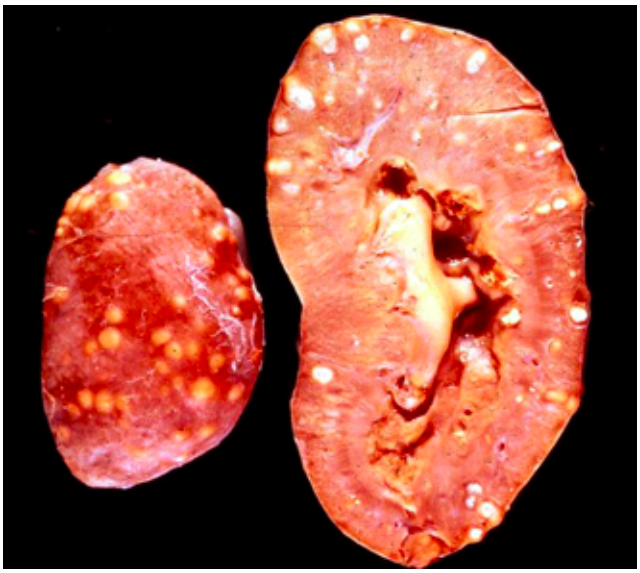

FIGURE 2: Cut gross specimen shows multiple predominantly peripheral white tuberculosed granulomas.

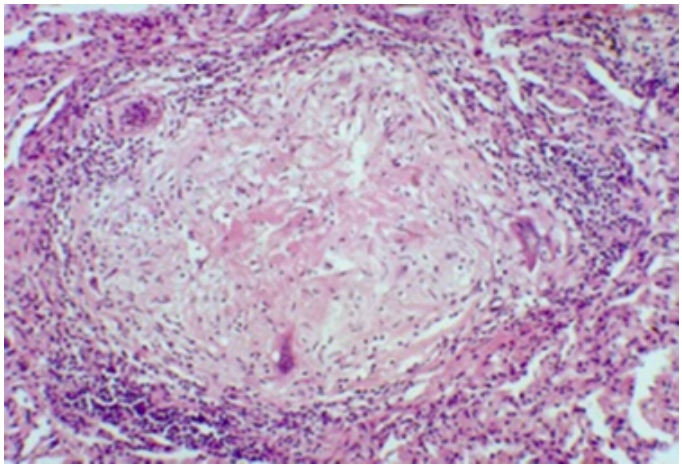

FIGURE 3: TB granuloma showing central necrosis (caseating granuloma) and the presence of giant cells.

**Investigations**

*Tuberculin Skin Test*: The tuberculin skin test measures a patient's cell-mediated immune response to a solution containing *M tuberculosis* antigens referred to as purified protein derivative (PPD). The test consists of intradermal injection on the inner surface of the forearm and the test is read 48 to 72 hours after administration. The area of induration is measured in millimeters with several criteria used depending on the patient (see Table 2).

*Table* 2. **Interpretation of Tuberculin Skin Test Results: Criteria for Tuberculin Positivity by Risk Group, According to Size of Induration, in Millimeters***

| ≥5 | ≥10 | ≥15 |
|---|---|---|
| HIV-positive persons<br>Recent contacts of persons with active TB<br>Persons with fibrotic changes on chest X-ray consistent with old TB<br>Patients who have had organ transplantation and other immunosuppressive conditions (receiving equivalent of ≥15 mg prednisone/d for >4 wk) | Recent (<5 y) arrivals from high-prevalence TB countries<br>Injection drug users<br>Residents or employees of high-risk congregate settings, such as prisons and jails, nursing homes and other long-term facilities for elderly persons, health care facilities, residential facilities for AIDS patients, homeless shelters<br>Persons with comorbid conditions that place them at high risk for TB (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, some intestinal conditions)<br>Mycobacteriology laboratory personnel<br>Children aged ≤4 y | Persons with no risk factors for TB |

*TB = tuberculosis.*
** Data from reference 2.*

Table 2: Tuberculin test results interpretation [7]

*Routine Tests:* Routine tests include complete blood cell (CBC) count, erythrocyte sedimentation rate (ESR), serum chemistry, and C-reactive protein (CRP) studies. Together these tests are used to detect severity of the disease, renal function and response to treatment. CBC is a panel of tests, which used to evaluate the patient's white blood cells, red blood cells and platelets. ESR is a non-specific test, which is used to detect inflammation associated with infection and once normalized can be used when the patient is on therapy. CRP is also a non-specific indicator of inflammation but the results used together with signs and symptoms can differentiate acute from chronic inflammatory conditions [8]. Basic metabolic panel (BMP) is a group of tests used to assess patient's renal function, electrolyte and acid/base balance alongside blood glucose and calcium levels.

*HIV Test:* HIV positive individuals are at a greater risk of developing TB and the infection may be ruled out at the discretion of the attending physician. There are several HIV antibody tests used in screening (HIV-1 and HIV-2) and combination antibody/antigen tests (p24 antigen) have been developed.

*Urine Tests:* Urine studies include urine cultures for acid-fast bacilli as well as urinalysis. Genitourinary findings include microscopic hematuria, albuminuria or sterile pyuria and if detected should be further investigated since this is not a definitive method of diagnosis [9].

*Polymerase Chain Reaction (PCR) and DNA Probes:* PCR is highly sensitive, specific and rapid, which is very important in TB infection so as to not delay appropriate treatment. The PCR tests currently used include: genus-specific 16S rRNA, species-specific IS6110, Roche Amplicor MTB and amplified *M tuberculosis* direct detection test (AMDT). DNA probes differentiate between different species of Mycobacteria. *M tuberculosis* also relies on culture and AFB staining results of semen and urine. Radiometric media: The BACTEC 460 medium yields results in 2-3 days

*Radiography:* Radiography studies include a technique, which uses electromagnetic radiation (X-rays) to visualize internal parts of the body. X-rays of the chest and spine are done and the findings may include old or active pulmonary TB lesions, although in ~50% of the cases these findings are negative. Intraluminal calcifications are revealed on X-rays of the kidney, ureter and bladder (KUB) in ~50% of the patients, while calcifications in the bladder are rarely seen. Computerized tomography (CT) scanning with contrast in conjunction with intravenous pyelography (IVP) (also referred to as intravenous urography or IVU) is used to assess the function of the kidney and the extent of the disease in late stage of GUTB [10]. Calcifications in

the ureter and bladder are detected with high sensitivity using IVP. Advanced disease presents with no visualization of the affected kidney via excretory urography.

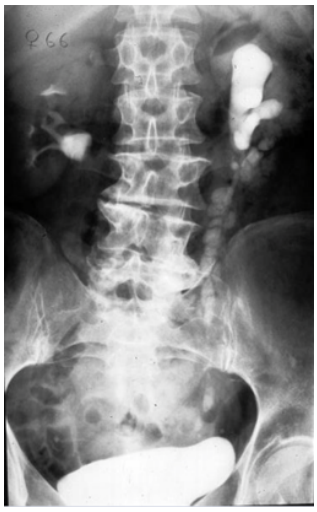

FIGURE 4: Intravenous Urogram

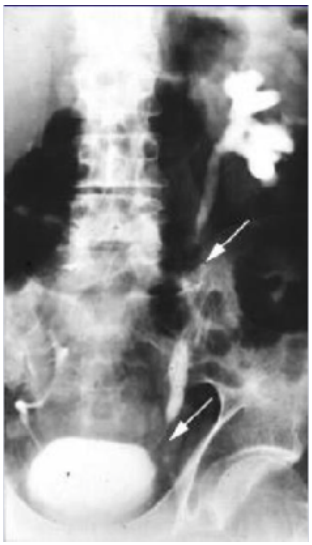

FIGURE 5: Intravenous Pyelogram. Left blunting of the calyces (caliectasis) and two long ureteral structures (arrows) [11].

**Treatment**

| Treatment of TB (World Health Organization Recommendations) | | |
|---|---|---|
| Category of TB | Initial Phase* | Continuation Phase |
| New cases of smear-positive TB<br>Severe smear-negative TB<br>Severe concomitant HIV disease | 2 months $H_3R_3Z_3E_3$ or 2 months $H_3R_3Z_3S_3$<br>2 months HRZE or 2 months HRZS | 4 months $H_3R_3$<br>4 months HR<br>6 months HE[ł] |
| Previously treated smear-positive TB<br>Relapse<br>Treatment failure<br>Treatment after default | 2 months $H_3R_3Z_3E_3$ or 1 month $H_3R_3Z_3E_3$<br>2 months HRZES or 1 month HRZE | 5 months $H_3R_3E_3$<br>5 months HRE |
| New cases of smear-negative TB | 2 months $H_3R_3Z_3E_3$<br>2 months HRZE | 4 months $H_3R_3$<br>4 months HR<br>6 months HE[ł] |

*subscript following the letter refers to the number of doses per week; daily has no subscript (H=isoniazid; R=rifampin; Z= pyrazinamide; E= ethambutol; S= streptomycin)

[ł]A continuation phase of 6 months HE has a higher failure and relapse rate than a continuation phase of 4 months of HR but can be used for mobile patients and those with limited access to health services; the HE regimen can also be used concomitantly with antiretroviral treatment of HIV infected patients.

Treatment should be guided by sensitivity testing.

Ethambutol may by omitted in the initial phase of category 3 patients if disease is non-

| |
|---|
| cavitary, smear-negative TB, or if patients are known to have a drug-susceptible organism, or for young children with primary TB. |

TABLE 3: Treatment of TB (World Health Organization Recommendations) [12]

The 6 month anti-mycobacterial treatment plan for genitourinary tuberculosis includes a 2 month intensive phase aimed to destroy all bacilli and a 4 month continuation that aims to prevent relapse. This 6 month treatment plan is seen to be more cost effective, however it may promote multidrug resistance.

In addition to drug treatment for GUTB, surgical treatment can be effective in extensive cases. When pain fails to subside, there are recurrent secondary bacterial infections, or hypertension develops, excision of the affected tissue may be indicated [13]. Reconstructive surgery is indicated in cases involving ureteric or urethral strictures.

| Main adverse reactions of first-line antituberculous drugs | | | | | |
|---|---|---|---|---|---|
| | Isoniazid | Rifampicin | Pyrazinamide | Streptomycin | Ethambutol |
| Mode of action | Cell wall synthesis | DNA transcription | Unknown | Protein synthesis | Cell wall synthesis |
| Major adverse reactions | Peripheral neuropathy[1]<br>Hepatitis[2]<br>Rash | Febrile reactions<br>Hepatitis<br>Rash<br>Gastrointestinal disturbance | Hepatitis<br>Gastrointestinal disturbance<br>Hyperuricemia | 8th nerve damage<br>Rash | Retrobulbar neuritis[3]<br>Arthralgia |

| | | | | | |
|---|---|---|---|---|---|
| Less common adverse reactions | Lupoid reactions<br>Seizures<br>Psychoses | Interstitial nephritis<br>Thrombocytopenia<br>Hemolytic anemia | Rash<br>Photosensitization<br>Gout | Nephrotoxicity<br>Agranulocytosis | Peripheral neuropathy<br>Rash |

[1]The risk of peripheral neuropathy may be reduced by prescribing pyridoxine.

[2]Hepatitis is more common in patients with a slow acetylator status and in alcoholics.

[3]Reduced visual acuity and color vision may be reported with higher doses and are usually reversible.

TABLE 4: Main adverse reactions of first-line antituberculous drugs

**Conclusion**

TB is an infectious disease caused by *M. Tuberculosis* affecting the lungs primarily. However, it can spread to extrapulmonary organs by hematogenous dissemination including the genitourinary system. Hematogenous dissemination of MTB occurs from a primary TB focus within the lungs, bone, or other organs and can involve both kidneys. Bacille Calmette-Guerin (BCG)–a live, vaccine strain–can cause renal lesions via reflux, in 0.1% of patients undergoing intravesical instillation of BCG for the treatment of bladder cancer. Various factors can increase the incidence especially immunocompromised patients. Urogenital TB affects the kidneys with urethral and bladder following through the urinary collecting system and taking a descending route. The renal TB noted as primary site as described in adults seem to develop tuberculous epididymoorchitis caused by direct spread from the urinary tract [14]. Symptoms arise when there is a bladder impairment with dysuria and hematuria being the most common signs and symptoms. PCR for *M. Tuberculosis* in the urine has become the diagnostic tool. An anti-tuberculosis drug regimen treatment is required for GUTB. There are 6, 9, 12 month regimen. The drug treatment regimen is very specific and tailored to each patient. Immunocompromised

patients such as HIV/AIDS patients a 9-12 month treatment is needed. Surgery may be performed with removal of tuberculosed organ following a 4 to 6 week medication regimen.

References


1. Abbara, A., Davidson, R. (2011). Etiology and Management of Genitourinary Tuberculosis. *Nature Reviews Urology* 8(12), pp.678-688. Retrieved from https://www.nature.com/articles/nrurol.2011.172

2. Figueiredo, A., Antonio, M., Renato, F., Srougi, M. (2008) Epidemiology of Urogenital Tuberculosis Worldwide. *The International Journal of Urology* 15(9): 827-32. Retrieved from https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1442-2042.2008.02099.x

3. Kapoor, R., Ansari, M., Mandhani, A., Gulia, A. (2008). Clinical Presentation and Diagnostic Approach in Cases of Genitourinary Tuberculosis. *NCBI Journal*. Vol 24(3): 401-405. DOI: 10.4103/0970-1591.42626

4. Visweswaran, R., Pais, V., Dionne-Odom, J. (2017). Urogenital Tuberculosis. *UpToDate*. Retrieved from https://www.uptodate.com/contents/urogenital-tuberculosis#H4742064

5. Meena, L., Ansari, R. (2017). Pathogenic Aspect of Genitourinary Tuberculosis in Males and Females. Journal of Molecular Biology and Biotechnology Vol 2(1). Retrieved from http://www.imedpub.com/articles/pathogenic-aspects-of-genitourinary-tuberculosis-in-males-and-females.php?aid=18341

6. Adhikari, E., Duryea, E., Rac, M., Sheffield, J. (2014). Genitourinary Tuberculosis: A Rare Cause of Obstructive Uropathy in Pregnancy. *Case Report in Obstetrics and Gynecology* V2014: 1-4. DOI: http://dx.doi.org/10.1155/2014/985682

7. Jacobson, K. (2017). Tuberculosis. *Annals of Internal Medicine*. Retrieved from http://annals.org/aim/article-abstract/2601211/tuberculosis

8. Figueiredo, A., Lucon, A. (2008). Urogenital Tuberculosis: Update and Review of 8961 Cases from the World Literature. *Reviews in Urology*, *10*(3), 207–217. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2556487/

9. Bharati, A., Merchant, N., Merchant, S. (2013). Tuberculosis of the Genitourinary System - Urinary Tract Tuberculosis: Renal Tuberculosis. *Indian Journal of Radiology and Imaging* V23(1), 46-63. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23986618

10. Bell, D., Gaillard, F. (2016). Genitourinary Tuberculosis. *Radiopaedia Journal*. Retrieved from https://radiopaedia.org/articles/genitourinary-tuberculosis

11. Merchant, S., Bharati, A., Merchant, N. (2013). Tuberculosis of the Genitourinary System - Urinary Tract Tuberculosis: Renal Tuberculosis. Indian Journal of Radiology and Imaging. Vol 23(1): 46-63. Retrieved from

http://www.ijri.org/article.asp?issn=0971-3026;year=2013;volume=23;issue=1;spage=46;epage=63;aulast=Merchant

12. Kulchavenya, E., Naber, K., Bjerklund, T. (2016). Urogenital Tuberculosis: Classification, Diagnosis, and Treatment. *Elsevier European Urology Journal*. Vol 15(4): 112-121. DOI: https://doi.org/10.1016/j.eursup.2016.04.001

13. Kulchavenya E. (2013). Best Practice in the Diagnosis and Management of Urogenital Tuberculosis. *Therapeutic Advances in Urology* Vol 5(3): 143-151. DOI:10.1177/1756287213476128.

14. SV Jagtap, DB Nikumbh, et al (2012). Classical renal tuberculosis presented as recurrent sterile pyuria and end stage kidney. *International Journal of Health Science & Research* 2 (5), 127-132.