available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Urogenital Tuberculosis: Classification, Diagnosis, and Treatment

Ekaterina Kulchavenya [a,*], *Kurt Naber* [b], *Truls E. Bjerklund Johansen* [c]

[a] *Urogenital Department, Novosibirsk Research TB Institute, Novosibirsk Medical University, Novosibirsk, Russian Federation;* [b] *Technical University, Munich, Germany;* [c] *Urology Department, Oslo University Hospital, Oslo, Norway, and Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark*

Article info

Keywords:
Antituberculosis drugs
Bacillus Calmette-Guérin therapy
BCG-induced complications
Bladder tuberculosis
Chemotherapy
Kidney tuberculosis
Prostate tuberculosis
Urogenital tuberculosis

Abstract

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.

* Corresponding author. Okhotskaya 81-a, Novosibirsk 630040, Russian Federation.
Tel. +7 383 2037989; Fax: +7 383 2038657.
E-mail address: ku_ekaterina@mail.ru (E. Kulchavenya).

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,

http://dx.doi.org/10.1016/j.eursup.2016.04.001
1569-9056/

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 anthropozoonotic infection.

Bacillus Calmette-Guérin (BCG), which is in fact an attenuated *M bovis*, is widely used for therapy of superficial bladder cancer. In some conditions 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 tubercle-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