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Epidemiology, classification, clinical features, and diagnostics of urogenital tuberculosis

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Abstract

Tuberculosis of the kidney, urinary tract and genital tracts (male and female) has followed mankind's history. During the last century, the number of cases of tuberculosis, pulmonary as extra-pulmonary, has decreased with the social and economic developments. However, in low and middle income countries the trend is still to an increase in the incidence of the disease, especially in populations associated with immunocompromised conditions (e.g. HIV). Large migration of population over the world is also a reason for meeting unexpected new cases in communities where this old disease was almost eradicated. Therefore, it is important for all urologists and physicians to be aware of tuberculosis as a possible differential diagnosis and have the basic know-how for identifying and diagnosing the communicable disease.

Summary of recommendations

1. Urogenital tuberculosis (UGTB) must be considered as a differential diagnosis in case of non-typical clinical symptoms and signs of the urinary and genital tracts (GoR A).
2. History is very important for the diagnosis of UGTB (GoR A) as about half of all patients with UGTB have a past history of primary site tuberculosis, mostly pulmonary (LoE3).
3. In up to 90%, UGTB patients have abnormal urinalysis. Pyuria with or without hematuria and negative standard non-specific urine culture ("sterile pyuria") is the typical finding at urinalysis (LoE3).
4. Imaging of the urinary tract can be helpful in the diagnose of UGTB (GoR A).
5. To detect *M. tuberculosis*, the culture and/or NAATs are recommended (GoR A).
6. The Mantoux test and interferon-gamma release assays (IGRAs) are used for supporting diagnosis (GoR B).

1 Introduction

Tuberculosis (TB) remains one of the world's deadliest communicable diseases and is of a major global public health concern. According to the World Health Organization (WHO), there was a steady increase of the incidence of TB infected people from 8.6 million to 9.6 million during the years 2012–2014. The estimated mortality increased as well from 1.3 million to 1.5 million, of which almost one third were HIV-positive [1], [2], [3], [4]. WHO has recognized TB as not only a medical condition but a disease having an important social and economic impact. It has also an impact on reproduction [5]. Given the fact that most deaths from TB are preventable, the death toll from the disease is unacceptably high.

The aim of this chapter is to assist the urologists and other physicians to understand and be aware of an infectious condition that is rare outside countries with high endemicity or epidemic situations, presenting with great variation in symptoms and clinical signs and therefore also difficult to diagnose. This report reflects principally the experience from Asian and Central Asian countries.

2 Terms and definitions

TB is a multisystem disease with a large spectrum of presentation and manifestations. It can affect any

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organ or tissue, with pulmonary TB (PTB) being the main primary organ site. Extra-pulmonary TB (EPTB) indicates that other tracts than the pulmonary one is infected by TB.

Porter was the first to propose the term *urogenital TB* in 1894 [6]. Wildbolz suggested in 1937 the term *genitourinary TB* [7]. The term *urogenital TB* (UGTB) is more reasonable, because kidney TB is the most relevant and diagnosed more often than genital TB. Only about half (53%) of the patients with kidney TB will develop genital lesions, while about 62% of the patients with epididymitis/orchitis and 79.3% of that patients with TB of the prostate will present with a renal lesion as well [8], [9].

Actually, the term UGTB is not perfect either, because it includes kidney TB and male genital tuberculosis (MGTB) – with different clinical features and approaches to management.

However, presently, it is the most accepted term in use [10], [11].

Urogenital tuberculosis (UGTB) – infectious inflammation of urogenital system organs in any combination, caused by *Mycobacterium tuberculosis* (*Mtb*) or *M. bovis*.

2.1 Urinary tract tuberculosis includes kidney TB and urinary tract TB

Kidney tuberculosis (KTB) – infectious inflammation of kidney parenchyma, caused by *Mtb* or *M. bovis*

Urinary tract tuberculosis (UTTB) – infectious allergic inflammation of calyx (calyces), kidney pelvis, ureter and/or bladder caused by *Mtb* or *M. bovis*.

2.2 Genital tract tuberculosis (male, female)

Genital tuberculosis (GTB) – infectious inflammation of the female or male genital organs – accordingly female genital tuberculosis (FGTB) or male genital tuberculosis (MGTB) caused by *Mtb* or *M. bovis*.

Generalized urogenital tuberculosis (gUGTB) – tuberculosis of kidney, urinary and genital tracts TB – male or female.

3 Epidemiology of urogenital tuberculosis

In the pre-antibacterial era, the prevalence of urogenital tuberculosis (UGTB) was huge. Every fifth urological hospitalised patient had UGTB and more than a third of all pyonephrosis was due to TB. In that time, UGTB was mostly diagnosed in young people, equally male and female [12]. Nowadays, UGTB is the most common form of extra-pulmonary TB in countries with high endemicity or epidemic TB, while it is rarely detected in countries with low incidence rates [13], [14]. In developed countries, the urogenital manifestation is responsible for more than 40% of extrapulmonary cases [15]. In Europe, UGTB is diagnosed more often in people coming from countries with endemic/epidemic TB than in the indigenous population (Lenk, 2011 [16]). Renal involvement by TB infection is underdiagnosed in most health care centers, and it can be both a part of a disseminated infection and a localized urogenital disease [17].

An example of study from the Central Asian region is worth to be presented as an example of the complexity of diagnosis and size of the problem. To estimate the prevalence and spectrum of KTB in children and teenagers in an epidemic region, the histories of 131 patients with UGTB in Siberia and 819 UGTB patients in Kyrgyzstan were reviewed [18]. In Siberia only two children and one teenager with UGTB were identified (2.3% among all the cohort of UGTB); all had KTB stage 1. In Kyrgyzstan 17 children and 21 teenagers were diagnosed with UGTB (4.6% of all UGTB patients). All had a long history, underwent surgical interventions, six had fistulae, and two teenagers had microcystis (bladder TB stage 4). KTB stage 1 was diagnosed in two children only, KTB stage 2 in four patients, KTB stage 3 in eight, and KTB stage 4 in three children. Thus, 64.5% patients were revealed in the late complicated stage [18].

The proportion of UGTB is very different depending on the region/country, epidemic situation, awareness and index of suspicion, co-morbidity, among others. Table 1 summarizes some of the reports from different countries and continents. The most commonly affected sites of extrapulmonary TB in Korea were pleura, followed by lymph nodes, gastrointestinal organs, bones and joints, central nervous system; UGTB was the last [19]. From 2006 to 2013 in Korea 135 patients with extrapulmonary TB were diagnosed; among them six only (4.4%) had UGTB [20].

Table 1: The place of UGTB in the spectrum of EPTB

Place	Country	Year	Reference
1st	Russian Federation	2010	[13]
2nd	Russian Federation	2013	[14]
	North America	2015	[22]
3rd	Poland	2013	[23]
	Portugal	2015	[26]
4th	France	2014	[21]
	Korea	2015	[19]
The last	Turkey	2015	[25]
	Bangladesh	2014	[28]

UGTB is the fourth most common manifestation of the disease, but it is often underestimated by clinicians because of few and non-specific symptoms and insidious disease course [21]. UGTB is the third most common form of extrapulmonary TB after pleural TB and lymphatic TB in North America [22].

Purely extrapulmonary tuberculosis was diagnosed in Poland in 2013 in 415 patients (5.7% of all registered cases). Most patients had pleural TB (142 cases), peripheral lymph node TB (104), urogenital TB (58; 13.9%) or bone and joint TB (44 cases) [23].

The most common sites of EPTB involvement in Turkey were lymph nodes (39.4%), followed by pleura (23.6%), peritoneum (9.9%) and bone (7.4%). UGTB was diagnosed in 5.4% [24]. UGTB contributes 15–20% of extrapulmonary TB [25]. UGTB is the third most common form of extrapulmonary tuberculosis, comprising 4–17% of extrapulmonary forms [26].

Over the last decades extrapulmonary locations of the disease have become more frequent due to the increased prevalence of acquired immune deficiency syndrome and the increased number of organ transplants [27]. Extrapulmonary TB became more common with the advent of infection with human immunodeficiency virus and by the increase in the number of organ transplantation, which also leads to immunosuppression of thousands of persons [17]. UGTB represents about 27% of all extrapulmonary localizations of TB and may be due either to a disseminated infection or to a primitive urogenital localization [27]. Renal involvement in TB can be part of a disseminated infection or a localized genitourinary disease [17].

In Bangladesh lymph nodes are the most common site of involvement (50%) followed by tubercular pleural effusion (15%) and virtually every site of the body can be affected by tuberculosis; the share of UGTB is minimal [28].

The results and distribution of EPTB in different populations as shown by table 1, indicates how importan it is for all physician to be aware of and keep the diagnosis of UGTB in mind, especially in patients with immunocompromised status and originating in countries with endemic/epidemic TB [17].

Tumor necrosis factor (TNF-)α inhibitors are widely used for rheumatoid arthritis (RA). However, there are several risks to use TNF-α inhibitors. Given the properties of TNF-α inhibitors, prevention and early detection of tuberculosis (TB) are especially important. Even among TNF-α inhibitors, the risk of TB infection differs according to each drug. The incidence of TB is lowest with etanercept [29].

The risk of tuberculosis (TB) is significantly increased in chronic kidney disease [30]. The link between chronic kidney disease and TB has been known for more than 40 years, but the interaction between these two diseases is still poorly understood. Dialysis and renal transplant patients appear to be at a higher risk of TB, in part related to immunosuppression along with socioeconomic, demographic, and comorbid factors [31], [32]. The place of UGTB within the total spectrum of EPTB is shown in table 1.

4 Clinical features

There are no specific clinical features for the diagnosis of UGTB. There is a great variation of symptoms and signs. UGTB should be suspected in the presence of otherwise not explained general fatigue, fever, flank, lumbar or back pain, lower abdominal pain, lower urinary tract symptoms such as dysuria and gross hematuria. Systemic symptoms are rare.

These symptoms are, however, not specific for UGTB. Similar symptoms can be seen in conjunction with any type of urinary tract infection, male accessory gland infection, kidney or bladder stone disease, unspecific abdominal abnormality among others. Also, there may be no symptoms at all. The similarity of clinical features between non-specific and specific infections is the reason for TB being labelled as the “great imitator” [22], [33], [34], [35].

In a recent review of clinical features related to UGTB, kidney was the most affected organ (64.9%) following ureter (27.35%), urinary bladder (17.09%), prostate (3.4%) and epididymis (5.19%) [36].

In a recent report from China, patients with renal tuberculosis represented almost 1% of the urological inpatients during a period of 11 years from 2000 to 2010. The incidence rates were higher in the 40–60 years old patients (45.61%). 12.5% were first revealed in very late stage – with contracted bladder [37]. The condition is therefore considered as low and the risk of underdiagnose is high.

In a review of the literature on the subject, it appears that most KTB 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%) are possible. Most patients with renal TB have sterile pyuria (i.e. pyuria in the absence of standard uropathogens/bacteriuria growth), which can be accompanied by microscopic hematuria [17]. The clinical features of UGTB depending on the form of the disease are shown in table 2 [9]. The most common presenting symptoms were urinary irritation (61.1%) and lumbago (49.2%). High proportions of microscopic hematuria (63.2%) and microscopic proteinuria (45.6%) were also observed. The positive rate for TB-DNA was 66.3%. The positive rate for culture was 13.1% and for smear it was 9.8%. The abnormal outcome rates of the computerized tomography, ultrasonography, intravenous pyelography, and the nephrogram were 76.9%, 70.1%, 29.8%, and 37.0%, respectively. The total rate of drug-resistant TB (resistant to at least one drug) was 39.7%, of which 20.7% was multidrug resistance TB [38].

Extracted Table: Table 2

Ureter and bladder TB is secondary to descending infection and the presentation is variating from no symptoms or signs at all to sever obstruction and calcification of the urinary tract. The bladder TB is mostly diagnosed in association with symptoms of cystitis, obstruction of the upper urinary tract, pyuria and hematuria.

Prostate tuberculosis is an infrequent manifestation of UGTB. Complications like prostate abscess, perineal fistula, sinus can occur in immunocompromised individuals [39]. Prostate TB may be asymptomatic and as an incidental prostatectomy finding. Prostatic abscess is rare but occur in AIDS patients with UGTB. Prostatic TB cavities or abscesses may discharge into the surrounding tissues, forming sinuses or fistulae to the perineum or rectum and are demonstrated best on MRI scans [25].

Prostate TB manifests by perineal pain and dysuria, and in half of the cases by hemospermia. TB epididymo-orchitis always starts from epididymitis, isolated TB orchitis is not reported. Oedema and

swelling of the scrotal organs and pain are most often the first symptoms, in 68% there is an acute debut of the disease. Nevertheless, in 32–40% the disease has a chronic or asymptomatic course [5], [40], [41], [42].

5 Diagnostics

The diagnosis of UGTB is often difficult and is based on clinical, radiological imaging, bacteriological and histopathological findings. Extrapulmonary lesions are paucibacillary and samplings, in some cases, difficult to obtain, making the diagnosis often simply presumptive [43]. The physician has to estimate the risk of TB exposure based on the patient's country of origin, chronic urinary tract symptoms and persistent sterile pyuria despite antibacterial therapy [44]. UGTB should be ruled out in a case of painless hematuria and repeated sterile pyuria [45].

The diagnosis of UGTB is difficult because the symptoms of the "great imitator" UGTB are similar to other inflammatory, infectious and malignant conditions of the kidney and urinary tract.

5.1 History

The diagnosis is therefore based on the history (anamnesis) and a series of examinations.

The risk of exposure and the known risk factors for UGTB should be evaluated carefully.

5.2 Physical examination

The physician has to carefully examine the patient with regards to the upper and lower urinary tract, respectively. The genital organs are examined systematically and a special attention is paid to the presence of perineal and scrotal fistula. In acute course of TB epididymitis, the epididymis is hard, tightly attached to the testis and be understood as a large, painful tumour like enlargement. In chronic course of the disease, epididymis is hard, enlarged, and painless with usually a palpable distinct border with the testis; in 35–40% the lesion is bilateral. Digital rectal examination of the patient with prostate TB shows possibly a moderate enlarged tuberous prostate gland with a weak tenderness. Again, scrotal and perineal fistulae are highly suspicious of TB [23].

5.3 Laboratory findings

5.3.1 History

UGTB is difficult to diagnose in the earlier stage owing to the non-specific symptoms. Usually, KTB involvement is unilateral and the imaging finding is renal calcification, but associated calcifications of bilateral ureter and bladder are rare. Chen et al. described a case of a 66-year-old man who presented with diffuse calcification of the urinary system (including bilateral pelvicalyceal system, both ureters and bladder) and disseminated miliary TB due to UGTB. He had been misdiagnosed with urinary tract infection and urinary lithiasis for two years before the diagnosis of UGTB was confirmed by microbiological examination of the urine [46].

5.3.2 Urinalysis

Up to 90% of UGTB patients have abnormal urinalysis. The majority of patients have pyuria with or without hematuria [27]. The standard urine culture is mostly without growth of uro-pathogens, which has given the term "sterile pyuria", a typical findings in UGTB. Hematuria is observed in about 50% of UGTB patients. UGTB should be considered in the presence of a persistent sterile pyuria [26]. The most common symptoms and signs were hematuria (79.7%), sterile pyuria (67.1%), dysuria (51.9%), weakness (51.9%), fever (43%) and costovertebral tenderness (38%). Histopathological verification of UGTB was achieved in 63.1% patients who undergone biopsy and in 100% of those undergone nephrectomy. Mycobacterium tuberculosis was isolated in the urine of 63.3% cases [47].

The difficulty in diagnosis is exemplified by a case presented by Biswas A and Meghjee SP [48]. An 18-year-old Caucasian male presenting with hematuria and loin pain. Peripheral blood testing demonstrated

renal failure, secondary to hydronephrosis, caused by hemorrhagic cystitis with no obvious cause for the obstruction. The patient was diagnosed with a urinary tract infection and treated with antibiotics. He responded well and his renal function improved. But four months later he re-presented with the above symptoms, weight loss and night sweats, bladder wall biopsy at this point confirmed tuberculosis [48].

5.3.3 Bacteriology

In “pre-antibacterial era” sterile pyuria was specific for KTB, but nowadays, up to 75% patients have non-specific pyelonephritis alongside with KTB, an image of mixed non-specific and specific chronic pyelonephritis. Uropathogens and *Mtb* may be found in urine at the same time [8]. The definite proof and evident diagnosis of UGTB is the detection of *Mtb*. For the diagnose of non-specific UTI a bacterial growth of not less than 103 CFU/ml is needed; to confirm UGTB, only one single *Mtb* is sufficient. [39]. During the last decade, remarkable progress has been made in the diagnostics of pulmonary TB; however, diagnostic challenges in UGTB remain important. The microbiological diagnosis of UGTB is difficult due mainly to the paucibacillary nature of disease, the need for invasive procedures to secure appropriate sample, and the lack of laboratory facilities in the resource limited settings [50]. When UGTB is suspected on clinical and imaging grounds, it is recommended to be generous with urine sample for *Mtb* identification in urine.

36% of patients on haemodialysis were positive for QuantiFERON Gold In-Tube test as compared to TST (17%). There was poor agreement between the two tests. No significant effect of BCG vaccination and history of TB in past was observed on both tests [51]. Among the different diagnostic modalities in this study, the diagnostic positivity rate was 41.6% for the urine AFB test, 55.4% for the urine *M. tuberculosis* culture test and 67.7% for PCR [36].

The definite diagnosis of UGTB is based on culture studies. Due to the paucibacillary nature of the disease, a probable or presumptive diagnosis is frequently considered with several parameters including radiological imaging (abdominal CT-scan, pelvic ultrasound, pelvic MRI). Endoscopic and surgical procedures are frequently required to obtain specimens for histopathologic and bacteriological studies [21].

Patients have non-specific symptoms and atypical presentations, which often lead to difficulty and delay in diagnosis. Urinalysis usually shows culture-negative pyuria and hematuria. A special acid-fast bacterial culture is required. Therefore, at least three first morning midstream urine samples are advised to isolate the organism. In addition, patients need to be off antibiotics at the time of urine collection since antibiotics may inhibit mycobacterial growth in culture g up to eight weeks for *Mycobacterium tuberculosis* to grow, with a false negative rate as high as 20% [22].

5.3.4 Histo-pathological examination

Histo-pathological examination (HPE), and bacteriology: acid-fast bacilli (AFB) smears, Lowenstein-Jensen (LJ) culture, BACTEC culture and polymerase chain reaction deoxyribonucleic acid (PCR-DNA). None of the available tests can pick up all cases of genital tuberculosis [52]. The Interferon-gamma release assay (IGRA) result was positive in 52.6% of UGTB patients. The results of the urine AFB stain and culture were positive in 8.8% and 12.2%, respectively. The results of UT-PCR were positive in 15.8%. Authors concluded, that the IGRA might feasibly be used as a supplementary or screening tool for the diagnosis of GUTB in addition to urine AFB stain and culture. Further studies for statistical evaluation of its sensitivity, specificity, and efficacy are needed [53].

5.3.5 Histological investigation

Histological investigation may reveal epithelioid granuloma, caseous necrosis, but they are fast replaced with fibrous tissue. If the patient was treated by fluoroquinolones and amikacin for “UTI”, which in fact masks UGTB, specific histological changes transform in fibrosis, and pathomorphological confirmation of the disease becomes impossible.

5.4 Imaging of the kidney and urogenital tracts

5.4.1 Ultrasound investigation

Ultrasound investigation may give indirect evidence of UGTB only. As prostate TB in 79% is accompanied by KTB, pathological changes detected by renal ultrasound in patient with “chronic prostatitis” are very suspicious for UGTB. TB epididymitis and orchitis present as diffusely enlarged lesions, which may be homogeneous or heterogeneous and can also present as nodular enlarged heterogeneously hypoechoic lesions [28].

5.4.2 Transrectal ultrasound investigation

Transrectal ultrasound investigation may reveal hypo- and hyperechoic lesions of the prostate, predominately in the peripheral zone; as well as zones with prostate stones which in fact may also be calcified zones of TB inflammation [29].

5.4.3 Complex radiography

Complex radiography is indicated for patients suspected for UGTB: plain X-ray films of the urinary tract may show calcification in the renal areas and in the lower urogenital tract; IVU is indicated for patients with leucocyturia and/or abnormality on ultrasound investigations. Imaging findings are also non-specific and may even further delay diagnosis. The astute clinician must have a high degree of suspicion for UGTB in patients presenting with non-specific symptoms, culture-negative pyuria, and for whom imaging studies seem atypical [22].

5.4.4 Tri-phasic CT

Tri-phasic CT remains the mainstay imaging study for cross-sectional imaging in renal TB, which can easily detect uneven dilatation of the caliceal system, strictures of calyceal necks, unexpected calcifications, and urothelial thickening. This imagine technique may also reveal calcifications, strictures or dilatations of the ureter, abnormalities in the urinary bladder or other unexpected anatomical or functional dysfunction.

Although these findings may be “typical” of UGTB, the differential diagnoses include partial staghorn stone, calyceal diverticulum with stones, chronic pyelonephritis, cystic renal cell carcinoma with calcification, fungal infections and urothelial carcinoma. Chest imaging may be abnormal in 40% to 75% of patients with UGTB. However, these abnormalities may be due to past tuberculosis and may not necessarily indicate active disease [22].

Retrograde urethrography should be performed in all patients with genital TB to exclude caverns of the prostate. X-ray examination is highly informative in cavernous forms of UGTB – both kidney (IVU) and prostate TB (urethrography), but multi-sliced computer tomography is significantly more informative. In 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 abscess. But UGTB on early stages has no specific radiological image.

Renal parenchymal cavities, hydronephrosis, ureteral stricture and thickened urinary tract walls were significantly more common on CT than on IVP. Multiple findings on CT were more common and very useful for TB diagnosis. CT looks like as the standard exam in patients with suspicion of urinary TB [47]. Hydronephrosis is a frequently observed radiological finding among patients with urinary TB. Most TB lesions were observed in the renal medulla, especially the dorsal and lower poles of the medulla [42].

5.5 Instrumental procedures

Instrumental procedures for UGTB diagnostic have nowadays limited value.

5.5.1 Cystoscopy

Cystoscopy is indicated for all UGTB patients having dysuria. Persistent dysuria in KTB patient is the basis for diagnosis of bladder TB, even without histological confirmation, which may be obtained in 12% of the patients with bladder TB stage 4 only [20]. Any mucosal changes should be biopsied and investigated both by histology and by bacteriology. Absence of the specific findings does however not exclude the diagnosis of bladder tuberculosis.

5.5.2 Ureteropyeloscopy

Ureteropyeloscopy may accidentally reveal TB ulcers along the upper urinary tract during a diagnostic or therapeutic procedure (e.g. stone management).

5.5.3 Prostate biopsy

Prostate biopsy should be made only after urethrography for excluding caverns. Tissue of the gland should be investigated by histology and bacteriology, at least by PCR [6], [7].

5.5.4 Scrotal organs biopsy

Scrotal organs biopsy, FNAC may be useful in the diagnosis of TB of external male genitals [8]. However scrotal violation should be considered if the mass is malignant, and there were fatal complications after biopsies performed to non-treated patients with active UGTB due to fulminant generalization of TB.

5.6 Provocative tests

The Mantoux test is positive in more than 90% of TB patients, but it has no value in regions with a severe epidemic situation (e.g. China, Russia, India, Africa), where almost all adults are infected with *Mtb* and thus all have positive skin tuberculin test. New Diaskintest has high specificity, but low sensitivity, and is not recommended for diagnosis of UGTB. Subcutaneous tuberculin provocative test is recommended [15].

5.7 Therapy ex juvantibus

Therapy ex juvantibus may be 1 st type, when patient takes antibiotic which does not inhibit *Mtb* (fosfomycin, cefalosporins, and nitrofurantoin), and therapy ex juvantibus 2 nd type, when the patient takes 2–4 antibiotics which inhibit only *Mtb* (isoniazid, PAS, protionamid, etionamid, ethambutol, pyrazinamid). The patient with low grade of suspicious for UGTB should be treated with therapy ex juvantibus 1st type, a positive result allows to exclude the diagnosis UGTB. If there remains doubt about the etiology of UTI, therapy ex juvantibus 2nd type is indicated.

If there is no evidence of *Mtb* diagnosis UGTB may be made on the basis of skin-test, histological picture, caverns revealed by urography, sterile pyuria etc. [15].

6 Further research

Biofilms are more resistant to antibiotics and antimicrobial stressors than planktonic bacteria; however, only a limited number of standardized assays enable investigation of this phenomenon. Recent study utilized non-invasive and independent techniques, including isothermal microcalorimetry (IMC) and tunable diode laser absorption spectroscopy (TDLAS), to measure the effect of isoniazid on metabolic activity and respiratory capability of mature *Mycobacterium tuberculosis* H37Ra (an avirulent strain) and *Mycobacterium smegmatis* biofilms. Only minor changes in metabolic heat production and respiratory rates (O_2 and CO^2) for mature *M. smegmatis* biofilms after antibiotic exposure were detected. However, mature *M. tuberculosis* biofilms showed greater sensitivity to antibiotic treatment, with isoniazid exhibiting dose-dependent effects on metabolic activity and respiration. Specifically, treatment of *M. tuberculosis* biofilms with 250 μg/ml and 1 mg/ml isoniazid decreased the rate of heat production by 33% and 40%, respectively, oxygen consumption by 18% and 55%, respectively, and carbon dioxide production by 27% and 64%, respectively. These effects were prominent even after regrowth of antibiotic-treated *M. tuberculosis* H37Ra biofilms on fresh medium. These data therefore suggest that IMC and TDLAS are appropriate for drug susceptibility testing of mature biofilms, and these techniques may facilitate study of microbial resistance to antimicrobial compounds from a bioenergetic perspective [56].

7 Conclusion

Tuberculosis of the kidney and the urogenital tracts remains a diagnostic and therapeutic challenge. The traditional combination of consistent pyuria and “sterile” urine culture remains a cardinal entity. In atypical clinical cases, uncharacteristic anatomical and function disturbances, UGTB must be considered as a differential diagnosis, especially in immunocompromised patients, and should be investigated for UGTB with laboratory key methods (e.g. direct microscopy, PCR urine for TB) and imaging of the urinary and genital tracts. Evidence of *Mycobacterium tuberculosis* or *M. bovis* strains is necessary to prove the diagnosis.

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