

# Genitourinary tuberculosis: historical and basic science review: past and present

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## KEY WORDS

genitourinary tuberculosis ▶ history of medicine

## ABSTRACT

Genitourinary tuberculosis (GUTB) usually results from the reactivation of old, dormant tuberculous diseases by pathogens of the mycobacterium tuberculosis complex. GUTB is the second most common form of extrapulmonary tuberculosis, with more than 90% of cases occurring in developing countries. In GUTB, the kidneys are the most common sites of infection and are infected through hematogenous spread of the bacilli, which then spread through the renal and urinary tract. Patients with genital and urethral TB present with a superficial tuberculous ulcer on the penis or in the female genital tract develop mainly due to primary contact with mycobacterium exposure during intercourse or inoculation via goods or chattels contaminated with mycobacterium.

The diagnosis of TB of the urinary tract is based on the case history, the finding of pyuria in the absence of infection as judged by culture on routine media, and by radiological imaging. However, a positive yellow egg culture and/or histological analysis of biopsy specimens, possibly combined with the polymerase chain reaction (PCR), is still required in most patients to establish a definitive diagnosis of GUTB.

The standard antituberculous drug treatment should be administered initially for two months during the intensive phase with three or four drugs daily followed by dual continuation therapy for four months. Surgery as a treatment option in GUTB might be indicated in complicated urinary tuberculosis. After antituberculous treatment of GUTB, surveillance with regular follow-up visits over the next five years is recommended.

In cases of drug resistance, additional drugs and prolonged treatment are required. Furthermore, increasing rates of drug-resistant cases and co-infection with HIV pose challenges in the treatment GUTB and other forms of TB.

There have been references to TB in India around 2000 BC and indications of lung scarring identical to that of modern day TB sufferers found in preserved bodies (e.g. mummies). Also, a unique bacteriological finding of acid-fast bacilli was discovered in smears taken from a psoas abscess in the well-preserved mummy of an Incan child from around 700 BC, clearly documenting a case of TB of the lumbar spine. The aforementioned findings clearly suggest that TB has been a nuisance to many civilizations for thousands of years.

Around 460 BC, Hippocrates (460-370 BC) identified phthisis (from Greek, meaning consumption) as the most widespread disease of those times. Phthisis was almost always fatal. Hippocrates first observed tubercles ("phymata") in the tissues of cattle, sheep, and pigs. However, analogous findings in man were not described, since human autopsies were not performed in the Greek world at that time. Patients with phthisis were often nursed in the Temple Precinct, where they were treated with good food, milk, and physical exercise. The Hippocratic School considered pulmonary phthisis a hereditary, rather than infectious disease. They also failed to recognize a common entity between tubercles and consumption.

Due to the variety of symptoms, TB was not identified as a unified disease until the 1820s and was not named as tuberculosis until 1834 by Johann Lucas Schönlein of Würzburg (1793-1864). He coined the term "tuberculosis" to describe the affliction with tubercles. However, he did not recognize its oneness with scrofula and phthisis.

During the years 1839-1845, Dr. John Croghan, the owner of Mammoth Cave in Kentucky, brought a number of TB sufferers into the cave in hopes of curing the disease with the constant temperature and purity of the cave air. However, it was not until the introduction of the sanatorium that a cure for TB was imminent.

Around the middle of the 19<sup>th</sup> century, in 1855, Herman Brehmer appeared with his thesis: *Tuberculosis primis in stadiis semper curabilis (Tuberculosis, in primary stadium, is always a curable disease)*. He (1826-1889) opened the first TB sanatorium in Görbersdorf, Lower Silesia in the belief that even existing consumption would abate in an immune place. His lead was followed by dynamic movements in the development of such sanatoriums all over Europe; in Germany (Black Forest and Bad Honnef), in Switzerland (Davos, Leysin, and Montana), in Italy (Sodalo and Valtellina), in France (on the Plateau d'Assis in the Savoy Alps), by the sea at Berck sur Mer, and in Poland at Zakopane. Although these patients recovered surprisingly well during their sanatorium treatments, the long-term results were fairly depressing [1, 2].

## Contributors to diagnosis of TB

Genitourinary tuberculosis (GUTB) involving the kidneys, prostate, and testis was well described by G. L. Bayle in 1810. Also, in 1823, Howship emphasized the importance of bladder symptoms in renal tuberculosis. Rayer, in 1839, described miliary tuberculosis, TB abscess, ulcero-cavernous lesions and the accompanying changes in the renal pelvis, ureter, and bladder, as well as the spread to the prostate and seminal vesicles. At that time, TB was difficult to distinguish from other urinary tract infections and diagnoses made on clinical impressions were not always accurate.

## HISTORY

Tuberculosis (TB) has been present and known to mankind since ancient times. The earliest evidence of TB in men and animals is provided by bone findings – mainly fragments of vertebrae – showing the gibbus deformity typical of tuberculous Pott disease. The oldest examples of spinal TB, in the form of fossil bones, date back to about 8000 BC. A bone from the Neolithic period (ca. 5000 BC), found in the region of Heidelberg, likewise shows evidence of tuberculosis changes.



Fig. 1. Dr. Robert Koch (1843-1910).



Fig. 2. *Mycobacterium tuberculosis* in Ziehl-Neelsen stain (acid-fast bacilli).

In 1882, Robert Koch (1843-1910) isolated the tubercle bacillus and in 1883 *mycobacterium tuberculosis*, an acid-fast aerobic bacillus, was identified in samples of urine and sputum (Fig. 1). Koch's discovery revolutionized the diagnosis of urinary tuberculosis and allowed the natural history of the condition to be accurately followed (Fig. 2).

Another equally important contribution to the diagnosis of TB came in 1895, namely the discovery of X-rays by Wilhelm Conrad von Röntgen (1845-1923) (Fig. 3). With the aid of the rapidly evolving radiological techniques (radiographs of chest and skeleton, fluoroscopy, photofluorography, I.V. pyelography, tomography), the development, course, and severity of TB could now be accurately monitored and studied. The present ability to treat TB, even though it is slow, would be virtually unthinkable without Röntgen's and Koch's outstanding scientific achievements both of which were honored with the Nobel Prize [1, 2, 3].



Fig. 3. Prof. Wilhelm Conrad von Roentgen (1845-1923).

### Epidemiology

In TB, the most common causative organism is the human tubercle bacillus. Tuberculosis is spread mostly via the air. When people suffering from active pulmonary TB cough, sneeze, spit, or even speak they expel infectious aerosol droplets 0.5 to 5  $\mu\text{m}$  in diameter. A single sneeze can release up to 40,000 droplets. Currently, one third of the world's population has been infected with *Mycobacterium tuberculosis* and new infections occur at a rate of one per second.

In the United States the dangers of bovine TB had been clearly grasped even before the turn of 19<sup>th</sup> century. In 1908, Chicago introduced the compulsory pasteurization of milk. In 1917, a tuberculin mass-testing program was begun for cattle herds in the US. In contrast, in Europe this measure was not undertaken until the end of the 1930s. This was based on a fateful error by Robert Koch, who regarded *Mycobacterium bovis* as non-pathogenic to man. In the early 1950s, regulations were introduced requiring the systematic slaughter of tuberculin-positive cattle herds. Thanks to these measures the problem of gastrointestinal TB today no longer exists.

The registered number of new cases of TB worldwide roughly correlates with economic conditions – the highest incidences are seen in the countries of Africa, Asia, and Latin America and in the areas with lowest gross domestic products. The World Health Organization estimates that nine million people get TB every year, of whom 95% live in developing countries. An estimated two to three million people die from TB every year [1-7].

### The beginnings of tuberculosis treatment

In the early days, the management of patients with pulmonary TB consisted largely of rest, a high-calorie diet, and symptomatic pharmacological therapy. Attempts were made to treat the patients with stimulus therapy, tuberculin injections, and light. Eventually these methods were gradually abandoned in favor of surgical treatment.



Fig. 4. Dr. Leon Charles Calmette (1863-1933).

Attempts to vaccinate against TB date back to well before the discovery of antibacterial drugs. The BCG (bacilli Calmette-Guérin) immunization was first carried out in Paris in 1921, particularly in children at high risk of infection, and soon became popular throughout Europe (Fig. 4). BCG is considered one of the safest of all vaccines, except in immunosuppressed individuals, who may develop local or disseminated bovine TB. The surgical therapy of pulmonary TB patients consisted of immobilization of one lung or of each lung successively. Also, pneumothorax techniques were performed in many variations over the course of 40 years. The new era in the treatment of TB began in 1944 with the introduction of streptomycin.

In 1942, Prof. Selman Abraham Waksman (1888-1973) isolated many antibiotics including streptomycin. It was the first antibiotic effective against tuberculosis. He coined the term 'antibiotic'. For his outstanding scientific achievement, Waksman was honored in 1952 with the Nobel Prize.

A rapid succession of anti-TB drugs appeared in the following years. These were important because with streptomycin monotherapy, resistant mutants began to appear within a few months, endangering the success of antibiotic therapy. However, it was soon demonstrated that this problem could be overcome by using combinations of two or three drugs.

The next generations of anti-TB drugs included p-aminosalicylic acid in 1946, isoniazid in 1952, pyrazinamide (1954), cycloserine (1955), ethambutol (1962), rifampin (rifampicin; 1963), and so on. Regardless of the agent, two properties of anti-TB drugs have proven to be important: their antibacterial activity and their capacity to inhibit the development of resistance [1, 2, 3, 5].

#### Genitourinary tract tuberculosis

Hans Wildbolz (1873-1940) was the first person to use the term 'genitourinary tuberculosis' in 1937. GUTB is one of the most



Fig. 5. Some multi-drug-resistant tuberculosis bacteria grow only on rifampicin (electron-microscopic view) [18].

common late manifestation of an earlier symptomatic or asymptomatic pulmonary TB infection. Genitourinary TB is usually caused by metastatic spread of organism through the blood stream during the initial infection. This active disease results from the primary infection or a reactivation of the initial infection. A latency period ranging from five to 40 years between the time of the initial infection and the expression of genitourinary TB frequently occurs. Extrapulmonary sites account for 10% of TB cases. The most common form of GUTB is genitourinary disease, accounting for 27% (range, 14 to 41%) worldwide. In India the incidence of GUTB is nearly about 18%. Prolonged steroid use and immunosuppressive therapy may increase the risk of reactivation of dormant foci. Patients with confirmed GUTB should also undergo sputum testing.

GUTB, responsible for 30% to 40% of all extrapulmonary cases, is second only to lymph-node involvement. In developed countries GUTB occurs in two to 10% of cases of pulmonary TB; in developing countries these figures rise to 15 to 20%. GUTB affects more men than women (2:1), seldom children, with a mean age of 40.7 (range 5-90). In 26.9% of affected cases there is a non-functioning unilateral kidney and renal failure occurs in 7.4%. The prostate, epididymis, and seminal vesicles are also commonly involved.

Prostatic TB is also spread hematogenously, but it is rare; however, of those with affected prostates, 85% also have renal TB. The affected prostate is nodular and not tender to palpation. Severe cases may cavitate and form a perineal sinus, although this development is rare. Decreased semen volume may indicate extensive prostatic disease or ejaculatory duct obstruction. In men, the sites most commonly involved are epididymis, followed by the prostate. Testicular involvement is less common and usually is the result of direct extension from the epididymis. Tubercular prostatitis usually results from antegrade infection within the urinary tract. Many theories have been postulated to define the precise route of infection to the epididymis. These include infected urine spread via the lymphatic system and metastatic spread through the blood stream. Female to male transmission (venereal transmission of TB) is very rare.

Testicular involvement is usually as a result of local invasion from the epididymis, retrograde seeding from the epididymis, and rarely by hematogenous spread. Infertility may result from bilateral vasal obstruction. Nodular beading of the vas is a characteristic physical finding, but orchitis and the resulting testicular swelling can be difficult to differentiate from other mass lesions of the testes. Male genital tuberculosis is usually associated with renal TB in 60 to 65% of cases or with pulmonary TB in around 34% of cases.

Urethral TB is secondary to genital TB. In patients with genital and urethral TB, men present with a superficial tuberculous ulcer on the penis and females present with internal ulcerations of the genitalia secondary to mycobacteria exposure during intercourse.



The penile ulcer may cause cavernositis that extends to the urethra. Male genital TB is predominantly associated with tuberculosis of the kidney and prostate, seminal vesicle, epididymis, testes as well as scrotum may occasionally be affected. Involvement of scrotal wall suggests local extra-testicular extension of disease process.

In TB of the female genital tract, the bacilli reach the genital tract by three principal routes – the hematogenous route (90%), ascending direct spread, or by lymphatic spread. Primary infection of the genitalia may rarely occur from direct inoculation during sexual intercourse with patients with GUTB. Trans-serosal exudation may give rise to pelvic inflammatory disease and subsequently extensive pelvic diseases. Very rarely sexual transmission has been reported, as 3.9% men with GUTB harbor bacilli in semen. This form of TB may involve the uterus and fallopian tubes causing strictures. Malignancy should be considered if genital ulcers are present. Acute urethritis manifests with mycobacterial discharge and often results in chronic stricture formation.

It is estimated that 1% of infertile women aged between 20–40 years in the United States and 18% of women in India suffer from genital TB. In females the genital organs commonly affected are as follows: fallopian tube (95–100%), endometrium (50–60%), ovaries (20–30%), cervix (5–15%), myometrium (2.5%), and vulva/vagina (1%) [2, 4, 8, 9, 10].

### Diagnosis of GUTB

The presentation of genitourinary tuberculosis (GUTB) is often vague and physicians must have a high degree of awareness to make the diagnosis. Patient history is key in the evaluation of GUTB. A significant differential diagnostic overlap requires maintaining a high index of suspicion for GUTB in both men and women. Diagnosis is often delayed owing to the nonspecific nature of its presentation; therefore, a high degree of suspicion should be exercised and a systematic approach should be taken during investigation [4, 6, 8, 9, 10, 11].

### Treatment of GUTB

The pharmacological therapy of patients with genitourinary tract TB is analogous to lung TB. An initial 2-month treatment of daily isoniazid, rifampin, pyrazinamide, and sometimes ethambutol is followed by 4–months or 7–months of daily or twice weekly isoniazid and rifampin. Usually, after two weeks of treatment, no bacilli can be identified in urine.

Current guidelines recommended that AIDS patients with tuberculosis receive the same standard, short-course therapy as HIV-negative patients. A minimum of nine months treatment is recommended, because higher rates of relapse are associated with shorter regimens. Antiretroviral therapy complicates the management of tuberculosis. Almost all antiretroviral drugs have the potential for hepatotoxicity, as do isoniazid, rifampin, and pyrazinamide, and clinical and laboratory monitoring of patients receiving these therapies is indicated.

The early hopes that chemotherapy would cure all stages and variations of urogenital tuberculosis have not been realized. More difficult or complicated cases of GUTB are referred to surgery as a radical measure [4, 5, 6].

### Surgical treatment

Although chemotherapy is the mainstay of treatment, ablative surgery as a first-line management may be unavoidable in cases of sepsis or abscesses. Ablative surgery is generally associated with partial or total nephrectomy, nephro-ureterectomy, cystectomy, epididymectomy, semicastration, salpingectomy, as well as other procedures.

Nephrectomy is indicated by complications such as severe upper urinary tract infection with Gram negative or Gram posi-

tive bacteria, urinary stones, and hypertension. Extensive disease involving the whole kidney, non-functioning kidney with ureteropelvic junction obstruction, or coexisting renal carcinoma are strong indications for nephrectomy. For localized lesions in the kidney, partial nephrectomy became popular following Carl Semb's (1895–1971) demonstration in 1949, in which he described the effectiveness of this operation together with a protective course of chemotherapy.

In case of partial nephrectomy, cavernostomy has been used to treat closed abscesses. This procedure, first used by Werner Stehler (1908–1984) in 1954, consisted of aspirating the cavity, deroofting the lesion, removing the caseous contents, and instilling streptomycin. More recently, Hanley has closed the cavity – the operation of speleotomy (or cavernotomy) – with success.

Today, there are two indications for partial nephrectomy. The localized polar lesion with calcification that has failed to respond after six weeks of intensive chemotherapy and when the area of calcification is slowly increasing in size and is threatening to gradually destroy the whole kidney. Open surgical drainage of an abscess should not be attempted.

The pain and frequency of bladder tuberculosis were major problems in former days. Treatments included a variety of bladder instillations, irradiation of the vesical mucosa, and other methods that included hydrostatic dilatation and the application of silver nitrate or other cauteries, such as: boric acid, corrosive sublimate, iodoform in liquid paraffin, guaiacol in oil, picric acid, and carbolic acid. Also used, was the insufflation of iodine vapor into the bladder by means of a catheter administered together with ultraviolet light. When all conservative measures failed, the vulnerable condition of the patient led to more drastic attempts to provide relief by cystostomy, artificial vesicovaginal fistula, nephrostomy, uretero-enterostomy, and/or total cystectomy. These were usually measures of last resort in patients with progressive disease and proved of little value [2, 3, 9, 11, 12, 13].

### Reconstructive surgery

Reconstructive surgery is considered for: ureteric or urethral stricture repair; stent placement, replacement, or reimplantation; resection; urinary diversion; and bladder augmentation cystoplasty.

Reconstructive surgery is frequently required for the repair of strictures of the ureter as well as for bladder augmentation in the case of a small fibrotic bladder. Early ureteral stenting or percutaneous nephrostomy in patients with tuberculous ureteral strictures may increase the opportunity for later reconstructive surgery and decrease the likelihood of loss of the kidney. The contracted bladder after chemotherapy rarely responds to conservative measures and once the infection has been brought under control, diversion of the urine by the formation of an ileal neobladder or enlargement of the bladder by ileocystoplasty or colcystoplasty may become necessary.

There are two indications for epididymectomy. The first is a caseating abscess that is not responding to chemotherapy. The second is firm swelling that has remained unchanged or has slowly increased in size despite the use of antibiotics and antituberculous chemotherapy.

Orchiectomy is seldom required. Ligation of the contralateral *vas deferens* is not needed. Epididymectomy should be performed through a scrotal incision. Both radical and reconstructive surgery should always be carried out in the first two months of intensive chemotherapy.

TB of the urethra is very rare. Patients should receive chemotherapy as initial treatment. In case of urethral stricture (stenosis), all possible and necessary surgical measures should be undertaken. The diagnosis of tuberculous prostatitis may depend on findings

that are made after transurethral resection of the prostate (TURP) when the pathologist reports foci of TB. The route of infection is via hematogenous spread of bacilli. These patients should be given antituberculous chemotherapy.

Mycobacterium TB infection of the penis has been reported, but it is very rare. These organisms were confirmed to be indistinguishable by the use of molecular techniques. At present, TB of the glans in adults is usually a primary or secondary (hematogenous) form. Primary TB of the penis occurs after direct sexual contact with bacillus already present in the female genital tract or by contamination from infected clothing or saliva. The diagnosis is confirmed by biopsy. These lesions generally rapidly respond to antituberculous chemotherapy.

Endometrial TB in the partner of a patient who had primary culture positive TB of the vulva and vagina is very rare and is seen in only 1% to 2% of genital tract TB. TB of the cervix accounts for 0.1 to 0.65% of all cases of TB and 5% to 24% of genital tract TB. Tuberculosis more frequently affects the upper genital tract, namely the fallopian tubes and endometrium. It usually occurs in women of childbearing age.

GUTB is very uncommon in children because the symptoms of renal TB do not appear for three to 10 or more years after the primary infection. It is therefore unlikely that the disease will be seen in a child younger than five years. GUTB occurs in 4% to 15% of patients with TB and accounts for 73% of the cases of extrapulmonary TB. TB in children occurs most often in lower socioeconomic groups [4, 6, 7, 9, 14, 15].

#### Education of patients and their families on TB

Crucial education issues include long-term compliance, preventive measures, and early detection in other persons. In addition, patients should be advised to use condoms during intercourse. Sexual transmission of TB via infected semen has been reported to result in a vaginal TB ulcer. GUTB can be sexually transmitted until treatment clears mycobacteria from semen, urine, or other genital secretions. Mycobacteria usually clear approximately four weeks after appropriate medications are started.

#### Tuberculosis, a new global problem

Hopes that the disease could be completely eliminated has been hastened since the rise of drug-resistant strains in the 1980s. In the mid-1980s, both in industrialized and developing countries, the incidence and mortality due to TB started to rise again.

Tuberculosis remains a concern due to increasing poverty, migration of large groups of people, homelessness, and the spread of HIV. These factors contribute to the likelihood that a TB-infected individual will develop active tuberculosis. Tuberculosis and HIV are the leading causes of infectious disease-associated mortality worldwide. TB and HIV have been inextricably bound together from the onset of the HIV epidemic and globally one-third of HIV-infected persons are also infected with *Mycobacterium tuberculosis*.

GUTB has a different clinico-radiological presentation in immunocompromised patients. These patients present with a predominance of systemic symptoms, disseminated TB, multiple parenchymatous renal foci, and a lower frequency of lesions of the collecting system. In the context of immunosuppression, GUTB behaves as a severe bacterial infection with bacteremia, visceral metastatic foci, and formation of multiple organs abscesses. In HIV/AIDS patients prostatic abscesses has been also described, which may discharge spontaneously to the rectum, urethra, or perineum. The author of this paper consulted twenty years old AIDS patient with faintness, high speaking fever, urinary urgency, pseudoileus, and subvesical located mass. During the DRE the very

big, soft, fluctuating prostate was found, The big pocket of puss was perforated and spontaneously emptied. The patient recovered quickly for a time.

In industrialized countries this is a tragedy for the individuals concerned, but epidemiologically irrelevant.

In the third and fourth worlds, however, the impact of HIV infection on the TB situation, especially among young adults, is truly distressing. With proper treatment patients usually become non-infectious quite quickly, but a complete cure requires treatment for at least several months and, for instance, compliance with treatment schedules is one of the recurring problems faced in developing countries [3, 11, 15].

#### Medication resistance

Another main concern is that of drug resistance. Inadequate treatment or improper use of antituberculous medication remains an important cause for the development of drug-resistant TB. According to the WHO, more than half a million people die of tuberculosis. More and more antibiotics lose their effect against the TB bacteria. Currently about five percent of patients no longer respond to rifampicin and isoniazid, the two most important drugs in the treatment of the disease. Many people, especially in poorer countries are using the medicine too soon, because they are not aware of the consequences or they cannot pay for the agent. This promotes the emergence of resistant strains.

Primary resistance occurs when a person becomes infected with a resistant strain of TB. A person with fully susceptible TB may develop secondary (acquired) resistance during therapy because of inadequate treatment, not taking the prescribed regimen appropriately (lack of compliance), or using low-quality medication. Drug-resistant TB is a serious public health issue in many developing countries, as its treatment is longer and requires more expensive drugs. Multi-drug-resistant TB (MDR-TB) is a form of TB resistant to two or more of the primary drugs (e.g. isoniazid and rifampin) used for the treatment of TB. Extremely drug-resistant TB (XDR-TB) is TB resistant to both of the first line drugs (isoniazid and rifampin), any fluoroquinolone from the second-line drugs, and at least one of three injectable drugs. These multi-drug resistant strains of bacilli cause an acute form of the disease that is extremely difficult and costly to treat and, therefore, can be fatal.

Totally drug-resistant TB, which was first observed in 2003 in Italy, but not widely reported until 2012, is resistant to all currently used drugs. Despite rapid increases in the reporting of data on drug resistance, a definitive answer to the question of whether the proportion of TB cases with MDR-TB is increasing, decreasing, or stable at the global level cannot yet be provided.

Reporting on surveillance of anti-tuberculous drug resistance must improve further and be considered an essential and fundamental element of TB surveillance. More recently BACTEC 460 radiometric media test has become popular because of its much shorter time to a result of 2-3 days. The technological advances now make the diagnosis of drug resistant TB easier, quicker, and more accessible, and also offer opportunities for rapid gains in global surveillance of drug-resistant TB. For this potential to be accomplished, anti-tuberculosis drug resistance surveillance must be prioritized by national TB control programs and funding agencies [5, 6, 15, 16, 17].

#### Inverted World: Some of TB bacteria strains grow only on rifampicin

As with many invasive bacteria, the improper use of antibiotics can lead to drug-resistant TB. Recently it was discovered that some strains of tubercle bacilli can only grow on rifampicin. A team led by Ying Zhang of the Johns Hopkins Bloomberg School

of Public Health in Baltimore had discovered a strain of TB bacilli in a patient in China with 'strange' tuberculosis. They report a case of rifampicin (RMP) dependent/enhanced MDR-TB isolated from a patient who had been treated with the WHO-recommended optional thrice-weekly treatment. The clinical and bacteriological features were documented. The RMP-enhanced tubercle bacilli, which grew poorly without RMP, but grew better in its presence, was isolated from a patient after diagnosed treatment failure. The bacterial culture, when grown without RMP, consisted of mixed morphologies of short, rod-shaped, acid-fast bacteria and poorly stained coccoid bacteria, however, the cultured bacteria stained as normal acid-fast rods when grown in the presence of RMP. The 35-year-old man did not improve after treatment with rifampicin, but on the contrary had gone from bad to worse. Only the use of another agent without the administration of RMP yielded improvement. When cultured in the laboratory, the bacteria hardly grew at all until rifampicin was added to the nutrient broth. The isolated RMP-enhanced bacteria harbored the common S531L mutation as well as a novel mutation, F584S in the *rpoB* gene. Treatment regimens containing RMP, or the more powerful rifapentine, paradoxically aggravated the disease, but its exclusion from the regimen led to treatment success in the patient.

The authors conclude: "This study highlights the potential dangers of continued treatment of MDR-TB with rifamycins that can occur due to delayed or absent drug susceptibility results and calls for timely detection of RMP-dependent/-enhanced bacteria in treatment failure patients by including RMP in culture media and removal of RMP from the treatment regimen upon detection." Unfortunately, the reason why these single-celled organisms are responding to the antibiotic in such a way is still unclear [18] (Fig. 5).

### A growing incidence

While wealthy nations with well-functioning healthcare systems can reasonably expect to keep TB under control, catastrophe looms elsewhere. GUTB is a worldwide disease with more destructive consequences in developing countries where the diagnosis is delayed and there is a higher frequency of renal failure, unilateral non-functioning kidneys, ablative surgeries, and contracted bladders.

GUTB in AIDS patients will become more frequent in the coming years. This will be the result of the growing AIDS epidemic and decreasing AIDS-specific mortality rates. Not to mention the fact that the AIDS-TB association remains a major global health burden.

It is absolutely imperative that support be given to research projects devoted to improving the diagnosis of GUTB, speeding up resistance testing, developing an effective TB immunization, and designing highly effective anti-TB drugs. The involvement and funding of national and international parties will be crucial in developing and implementing effective TB interventions. Otherwise, in the long term, we are likely to once again lose our grip in controlling "the white plague" [1, 5, 7, 16, 17].

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