

## Review Article

# Tuberculosis: an overview of current literature on types, diagnosis and drug therapy

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## ABSTRACT

Tuberculosis (TB) is an airborne infectious disease caused by organisms of the *Mycobacterium tuberculosis* complex. It is a global problem and increases in case rates are occurring not only in the developing countries of the world but also in several industrialized nations. There has also been an alarming increase in the number and proportion of cases caused by strains of *Mycobacterium tuberculosis* that are resistant to multiple first-line drugs. The increase in multiple-drug resistant tuberculosis has re-taught physicians about the importance of pursuing and ensuring treatment until cure. In many low-income and middle-income countries, TB continues to be a major cause of morbidity and mortality, and drug-resistant TB is a major concern in many settings. This article offers an overview of types, diagnosis and management of TB.

**Keywords:** Drug resistance, Drug therapy, Isoniazide, *Mycobacterium tuberculosis*, Rifampicin, Tuberculosis

## INTRODUCTION

Tuberculosis (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 people with the active respiratory disease.<sup>1</sup> In 2015, 10.4 million people affected with TB and 1.8 million died from the disease (including 0.4 million among people with HIV). Over 95% of TB deaths occur in low- and middle-income countries. Six countries account for 60% of the total, with India leading the count, followed by Indonesia, China, Nigeria, Pakistan and South Africa. In 2015, an estimated 1 million children affected with TB and 170000 children died of TB (excluding children with HIV). TB is a

leading killer of HIV-positive people: in 2015, 35% of HIV deaths were due to TB. Globally in 2015, an estimated 480 000 people developed multidrug-resistant TB (MDR-TB).<sup>2</sup>

TB incidence has fallen by an average of 1.5% per year since 2000. This needs to accelerate to a 4-5% annual decline to reach the 2020 milestones of the "End TB Strategy". An estimated 49 million lives were saved through TB diagnosis and treatment between 2000 and 2015. Worldwide, the rate of decline in TB incidence remained at only 1.5% from 2014 to 2015. Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals. Global Task Force on TB Impact Measurement framed goals to

ensure the best possible evaluation of whether or not they are achieved. To reach these goals World Health Organization (WHO) recommends the Stop TB strategy. The strategy comprises best practices in the diagnosis and treatment of patients with active TB, approaches to address major epidemiological and system challenges of today, and the promotion of research for innovations.<sup>2</sup>

India is the country with the highest burden of TB. The World Health Organization TB statistics for India for 2015 give an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 9.6 million. It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent TB rather than TB disease.<sup>3</sup>

### **Miliary tuberculosis**

Miliary tuberculosis, is a fatal form of disseminated TB characterized by tiny tubercles evident on gross pathology similar to innumerable millet seeds in size and appearance.

#### **Diagnostic approach**

Following criteria are useful for the diagnosis of miliary TB in the clinical setting:

- Clinical presentation consistent with a diagnosis of TB such as, pyrexia with evening rise of temperature, weight loss, anorexia, tachycardia and night sweats of greater than six weeks duration responding to anti-TB treatment.
- Classical miliary pattern on chest radiograph.
- Bilateral diffuse reticulonodular lung lesions on a background of miliary shadows demonstrable either on plain chest radiograph or high resolution computed tomography (HRCT).
- Microbiological, histopathological and/or molecular evidence of TB.

#### **Tuberculin skin test and interferon-gamma release assays**

A positive tuberculin skin test (TST) or interferon-gamma release assays (IGRA) result only indicates infection with *Mycobacterium tuberculosis* and does not indicate active disease. Tuberculin anergy is common in miliary TB and has ranged from 35%-74% and 20%-70% in various pediatric and adult series, respectively. In high burden TB countries, neither IGRAs nor TST have been found to be adequate in accurately identifying persons who will benefit from treatment of latent TB infection (LTBI) with high false positivity rates being reported for both. Further, even after completion of treatment, the PPD as well as IGRAs will still remain positive. A policy statement issued by the WHO and the European Centre for Disease Prevention and Control guidelines discourage the use of IGRAs in preference to TST, in areas where TB is highly endemic for the diagnosis of pulmonary or extra-pulmonary TB.<sup>4</sup>

### **Urogenital tuberculosis**

It refers to an infectious inflammation of any urogenital organ, isolated or in combination (kidney, 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.

Clinical features of urogenital TB are nonspecific and unstable and depend on many factors, which is one of the reasons for the late diagnosis. As a whole, kidney TB 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%) may occur. Prostate TB manifests as by perineal pain and dysuria and in half of the cases by hematospermia. TB epididymo-orchitis always starts from epididymitis; isolated TB orchitis does not exist. Edema swelling and pain of the scrotal organs are most often the first symptoms. In 68% of cases, there is an acute debut of the disease. In 32–40% of patients, the disease has a chronic or asymptomatic course

#### **Imaging (ultrasonography)**

Renal ultrasound may give indirect evidence of urogenital TB only. Because prostate TB is accompanied by kidney TB in 79% of cases, pathologic findings detected by renal ultrasound in patients with so-called chronic prostatitis are very suspicious for urogenital TB. TB epididymitis and orchitis present as diffusely enlarged lesions that may be homogeneous or heterogeneous and can also occur as nodular enlarged heterogeneously hypoechoic lesions. Transrectal ultrasound may reveal hypo- and hyperechoic lesions of the prostate, predominantly in the peripheral zone, but also as prostatic lithiasis, which in fact may be calcified zones of TB inflammation.<sup>5</sup>

### **Spinal tuberculosis (STB)**

#### **Clinical presentation**

The clinical presentation and findings of physical examinations depend on the site and stage of the disease, presence of complications, and constitutional symptoms. The most commonly reported symptoms are back pain, fever, body weight loss, neurological abnormalities, and night sweats. Additionally, the thoracic spine is the most

frequently involved segment. The complications after STB included syringomyelia, permanent neurological deficits, and spinal osseous defects. Paraplegia is the most devastating complication of STB. The incidence of neurological deficit varies from 23% to 76%.

#### *Clinical laboratory diagnosis*

STB diagnosis is confirmed by typical clinical presentation along with systemic constitutional manifestation, evidence of past exposure to TB or concomitant visceral TB, and neuroimaging modalities. Montoux skin tests and hematological investigations, such as complete blood count, erythrocyte sedimentation rate, enzyme-linked immunosorbent assay, and polymerase chain reaction (PCR), are also helpful in diagnosing STB. Bone tissue or abscess samples stained for acid-fast bacilli, mycobacterial organisms isolated from culture, and computed tomography (CT)-guided or ultrasonography guided needle biopsy or surgical biopsy are also widely used.<sup>6</sup>

#### **Endobronchial tuberculosis (EBTB)**

It is a sequelae of pulmonary tuberculosis (TB) that extends to the endobronchial or endotracheal wall causing inflammation, edema, ulceration, granulation or fibrosis of mucosa and submucosa. According to Chung classification, EBTB is classified into 7 subtypes by bronchoscopy findings:

- Actively caseating
- Edematous-hyperemic
- Fibrostenotic
- Tumorous
- Granular
- Ulcerative
- Nonspecific bronchitic

The lung examination revealed labored breathing with the use of accessory muscles, biphasic stridor, diminished breath sounds and mild expiratory wheezes in all lung fields. Laboratory evaluation was unremarkable with normal white blood cell count. Chest X-ray showed focal rounded airspace opacity in the left upper lobe consistent with the previous evaluations. CT-scan of neck revealed previous cavitating lesions in the left apex but no suspicious neck abnormality, mass, collection or adenopathy in the neck soft tissues. Bronchoscopy revealed 90% occlusion of the trachea with a small pin hole opening and tracheal web approximately 3 cm below the vocal cords.<sup>7</sup>

#### **Abdominal tuberculosis**

Abdominal tuberculosis denotes involvement of the gastrointestinal tract, peritoneum, lymph nodes, and solid viscera, e.g. liver, spleen, pancreas, etc. The ileum and cecum are the most common sites of intestinal involvement and are affected in 75% of cases. Other

locations of involvement are the ascending colon, jejunum, appendix, duodenum, stomach, oesophagus, sigmoid colon, and rectum. Multiple areas of the bowel can be affected.<sup>8</sup>

#### **Diagnosis**

Routine laboratory tests reveal mild anaemia and increased sedimentation rate in 50 to 80 percent of patients. The white blood count is usually normal.

#### *Ultrasonography*

Ultrasound is useful for imaging peritoneal tuberculosis.

#### **Cervical lymph node tuberculosis**

Cervical lymph node tuberculosis occurs as a result of hematogenous spread from a distant source, or in the context of disseminated TB. It is rarely the result of contiguous invasion. Tuberculous meningitis is the most common presentation of TB in the CNS. The nodes are often grouped and can become massively enlarged. They are usually asymmetrical in the neck. Although the nodes start as firm, they frequently break down to form a fluctuant abscess. They are sometimes painful and are not usually associated with systemic symptoms. Abscesses often discharge through the skin. Diagnosis can be made by direct examination of an aspirate of pus or a biopsy sent for histology, culture and sensitivity. Lymph nodes frequently enlarge during treatment, and this should not be regarded as treatment failure.<sup>9</sup>

#### **Tuberculosis of the pleura**

Pleural TB is often thought to be an early manifestation of TB. The pleural effusion can disappear without treatment, but when the diagnosis is made, the patient should be offered treatment to prevent relapse. Onset is insidious, and pleuritic chest pain is not necessarily present. Patients become breathless and experience sweats and fever. Chest X-rays usually show a large unilateral pleural effusion with or without pulmonary parenchymal changes. Diagnosis is confirmed by the finding of an exudative pleural effusion with a lymphocytosis and low glucose concentration. Direct smears for AFB are usually negative but cultures become positive in 25-75%. Elevated concentrations of adenosine deaminase and interferon-gamma in the fluid can provide useful supportive evidence.

Pleural biopsy is diagnostic when it reveals caseating granulomas. Differential diagnoses such as adenocarcinoma, malignant meso-thelioma, parapneumonic effusions and empyema can usually be distinguished by examination of the pleural fluid, computed tomography and video-assisted thoracic surgery. With treatment, the pleural effusion usually resolves completely. Patients frequently experience minor pleuritic chest pains during the healing process.<sup>9</sup>

### **Central nervous system tuberculosis**

TB meningitis makes up a small proportion of clinical tuberculosis but has high mortality and chronic morbidity. Diagnosis is based on typical features of meningeal inflammation, such as headache and fever developing over days or weeks. Focal neurological signs can develop. Cognition may be impaired, and the condition can proceed to coma and death. A lumbar puncture is used with the clinical history and examination for diagnosis. Patients with TB meningitis have a longer history of disease and a lower peripheral blood neutrophil count and tend to be younger with a lower cerebrospinal fluid (CSF) neutrophil count than patients with bacterial meningitis. In TB meningitis, CSF glucose concentrations are lower and protein concentrations higher than in viral meningitis. In HIV-positive patients, cryptococcal meningitis is an important differential diagnosis. In one study in Vietnam, almost half the patients with TB meningitis had died or were severely disabled 9 months after presentation. Tuberculomas frequently develop during or after apparently effective treatment, and spinal arachnoiditis, which can be associated with paraplegia, incontinence and chronic pain, is a potential late complication.<sup>9</sup>

### **Tuberculous pericarditis**

TB pericarditis usually has an insidious onset characterized by fatigue, dyspnea and systemic symptoms of infection. Physical signs particularly raised jugular venous pressure, hepatomegaly and peripheral edema, are related to right-sided cardiac congestion. Initially, there is usually a moderately large exudative pericardial effusion, but with time this can progress to a more fibrotic constrictive picture. Histology of a pericardial biopsy is very helpful in confirming the diagnosis.<sup>10</sup>

### **Osteoarticular TB**

This is usually the result of hematogenous spread of bacilli. The vertebral location is the most common. Initial symptoms are very non-specific, of slow onset with a lack of constitutional symptoms, so diagnosis is usually late. The patient has non-specific localized pain and discomfort. If the clinical picture progresses, it leads to the extension of the lesion to adjacent vertebrae and progressive kyphosis by destruction of the anterior vertebral body. In advanced cases the infection spreads to the adjacent soft tissue, causes cold abscesses or towards the back of the vertebra and can affect the spinal cord, causing compression, which sometimes requires urgent surgery. Less frequently, bone TB affects other regions, with an emphasis on the metaphyseal portion of the long bones. A special form of joint disease is called Poncet's syndrome, where the patient has stiffness, polyarticular pain and, occasionally, inflammation and edema. The diagnosis is by exclusion. Osteoarticular TB were screened for bacterial culture, mycobacterial culture and

in-house nested PCR. In addition, specimens were examined by imaging and histopathology.<sup>11</sup>

### **Lymph Node TB**

The most common location is in the lymph nodes of the neck and supraclavicular region. TB in this location develops after spreading by hematogenous or lymphatic route from a distant source but may also be directly via the lymphatic system from the oropharyngeal mucosa and related structures. A cervical tumour is the most common presentation. It is not usually accompanied by constitutional symptoms or fever. The nodes tend to grow gradually and are at first of rigid consistency and painless. With time, necrosis may occur, with fluctuating inflammation and formation of fistulas and draining of material. The disease is also known as scrofula. The nodes may remain and even increase in size in spite of effective treatment. Oriental races have a greater predisposition to TB in this location. The diagnosis was confirmed by biopsy because the clinical features were non-specific and radiographic features of the lesions were negative for pulmonary involvement. Histopathology of the lesion demonstrated multinucleated giant cells, especially Langhans giant cells and histiocytes. Ultrasound examination done on cervical lymph nodes exhibited the size of the expanded lymph nodes.<sup>12</sup>

### **Laryngeal TB**

This currently occurs in less than 1% of TB patients. It is produced primarily by local extension from the bronchial tree. Laryngeal TB is often associated with bacilliferous pulmonary TB and is therefore highly contagious. The diagnosis is confirmed with the identification of granulomatous inflammation, caseating granulomas, and acid-fast bacilli on histopathologic examination of biopsied laryngeal tissue. However, making the diagnosis difficult can be the presence of pseudo epitheliomatous hyperplasia, which mimics squamous cell carcinoma.<sup>13</sup>

### **Skin TB**

Is usually a manifestation of a systemic disease, although it may be acquired by direct inoculation or extension from a contiguous focus, as is the case with scrofula. The manifestations of skin TB depend on the patient's immune status. Lupus vulgaris is a form of presentation in immunosuppressed patients and can lead to chronic deformities. Tuberculosis verrucosa cutis is usually a more indolent form in patients with mild or moderate immunosuppression. The tuberculids (Bazin's indurated erythema, scrofulous lichen and papulonecrotic tuberculids) are other forms of presentation usually found in immune competent patients. Although the latter are traditionally attributed to immune reactions, the presence of DNA from *M. tuberculosis* has sometimes been shown.

Tuberculin skin test (TST) identifies individuals sensitized to Mtb. The test becomes positive in 2 to 10 weeks after the infection. This technique involves intradermal injection of tuberculin purified protein derivative materials (PPD) on the front surface of the left forearm, followed by reading after 48 to 72 hours when the size of induration is measured (Mantoux technique). Interferon-gamma release assays are serological tests that assess latent infection by measuring interferon-gamma

produced by T-cells in individuals who were exposed to Mtb antigens.

However, previous infections by environmental mycobacteria such as *M. marinum* and *M. kansasii* may produce false positive results. Other tests like Investigation of acid-fast bacilli in stained smear, Polymerase chain reaction (PCR) Currently there are two tests commercially available and approved by the FDA, QuantiFERON-TB Gold (QFT-G) and T-SPOT.TB.<sup>14</sup>

**Table 1: First line, second line and some third line drugs currently in use for the treatment of drug-susceptible and drug-resistant tuberculosis.**

Category and drug	Chemical description	Daily adult dose <sup>a</sup> (mg)	Efficacy
<b>Group 1: First-line oral drugs</b>			
Isoniazid, INH	Nicotinic acid hydrazide	300	Bactericidal
Rifampin, RMP	Rifamycin derivative	600	Bactericidal
Pyrazinamide, PZA	Nicotinamide derivative	2000	Bactericidal
Ethambutol, EMB	Ethylene dimino di-1-butanol	1200	Bacteriostatic
<b>Group 2: Second-line, injectable agents</b>			
Streptomycin, SM	Aminoglycoside	1000	Bactericidal
Kanamycin, KAN	Aminoglycoside	1000	Bactericidal
Amikacin, AMI	Aminoglycoside	1000	Bactericidal
Capreomycin, CAP	Cyclic polypeptide	1000	Bactericidal
Viomycin, VIO	Cyclic polypeptide	1000	Bactericidal
<b>Group 3: Second-line, fluoroquinolones</b>			
Ofloxacin, OFX	Fluoroquinolones	800	Bacteriostatic
Levofloxacin, LFX	Fluoroquinolones	750	Bactericidal <sup>b</sup>
Gatifloxacin, GFX	8-Methoxy- fluoroquinolones	400	Bactericidal
Moxifloxacin, MFX	8-Methoxy- fluoroquinolones	400	Bactericidal
<b>Group 4: Second line, oral agents</b>			
Ethionamide, ETA	Isonicotinic acid derivative	750	Bacteriostatic
Prothionamide, PTA	Isonicotinic acid derivative	750	Bacteriostatic
D-Cycloserine, CS	Serine derivative	750	Bacteriostatic
Terizidone, TRD	Serine derivative	750	Bacteriostatic
Para-amino salicylic acid, PAS	Para-amino salicylic acid	8000	Bacteriostatic
<b>Group 5: Third –line, oral agents</b>			
Linezolid	Oxazolidinone derivative	1200	Bactericidal
Amoxicillin-clavulanate, AMX-CLV	$\beta$ -lactum with $\beta$ -Lactamase inhibitor	2000-250	Bactericidal
Imipenem- clavulanate, IMP-CLV	Carbapenem with $\beta$ -Lactamase inhibitor	2000-250	Bactericidal
Meropenam- clavulanate, MEP-CLV	Carbapenem with $\beta$ -Lactamase inhibitor	3000-250	Bactericidal
Clofazimine, CFZ	Iminophenezine derivative	200	Bacteriostatic
Thiacetazone, TAC	Thiosemicarbazone derivative	150	Bacteriostatic

<sup>a</sup>Total daily adult dose for a tuberculosis patient weighing >51kg, <sup>b</sup>at high dose (1000 mg)

### Multiple drug resistance tuberculosis (MDR-TB)

MDR-TB is caused by Mycobacterium tuberculosis strains resistant to, at minimum, rifampicin (R) and

isoniazid (H). The cause of resistance can be multifactorial: improper treatment, transmission of bacteria in public, poor management of drug quality and supply and others.

Two paths leading to TB drug resistance are the following:

- Acquired drug resistance is an outcome of inadequate treatment, which allows selection of resistant mutant strains

- Primary drug resistance is a consequence of infection with a drug-resistant TB strain that developed resistance, when mutations occurred in genes, encoding drug targets or drug metabolism mechanisms.<sup>15</sup>

**Table 2: Some promising anti-tubercular drugs in various stages of development.**

Potential drug	Active or Pro-drug	Description	Cellular process inhibited	Stage of development
PA-824	Pro-drug	Nitroimidazo-oxazine	Mycolic acid synthesis	Phase II
OPC-67683	Pro-drug	Nitroimidazo-oxazole	Mycolic acid synthesis	Phase II
R207910	Active	Diarylquinoline	ATP synthesis	Phase II
SQ109	Active	Ethylenediamine derivative	Lipid/cell wall synthesis	Phase I
Compound 5	Pro-drug	Quinoxaline-oxide derivative	Unidentified	Preclinical
Compound 7 g	Unknown	Quinoline-isoxazole derivative	Unidentified	Preclinical

### Current therapy

The chemotherapy of TB will almost always involve a cocktail of drugs because of the unique nature of the bacteria. It is difficult to design a single drug that can simultaneously kill the actively replicating, semi-dormant and dormant populations of the bacteria.

Among the existing first line drugs, only pyrazinamide can effectively kill the slow growing population of the bacteria with minimum bactericidal effect on the fast growing population. The existing first line of treatment is the best available option for treating TB (shown in Table 1 and 2). The designing of new treatment regimens is very crucial to control the current spread of the TB which is the leading cause of death by a single, treatable, infectious disease.

### DISCUSSION

The genes and their target regions that are involved in mediating the resistance of *M. tuberculosis* to first line and important second line anti-TB drugs.<sup>4</sup> Isoniazid (INH), a pro-drug, has potent activity against actively dividing *M. tuberculosis*. INH is activated by the katG-encoded catalase-peroxidase. The molecular basis of resistance to INH is complex, as resistance-conferring mutations are found in several genes. High-level resistance to INH is mainly due to mutations within the katG gene, while mutations in the inhA regulatory region confer low-level resistance to INH in *M. Tuberculosis* isolates.<sup>16</sup> Rifampicin (RIF) binds to the rpoB-encoded  $\alpha$ -subunit of RNA polymerase and inhibits RNA transcription/protein synthesis. Mono resistance to RIF is rare except in patients with HIV-co infection or other underlying diseases. Because nearly 85-90% of RIF-resistant *M. tuberculosis* isolates are also resistant to INH, resistance to RIF is regarded as a surrogate marker for

MDR-TB. Approximately 90-95% of RIF-resistant *M. tuberculosis* isolates contain mutations within an 81-bp rifampicin resistance-determining region (RRDR) (spanning rpoB codons 507-533, Escherichia coli numbering system).<sup>5</sup>

Pyrazinamide (PZA), a pro-drug, is highly effective against semi-dormant bacilli in an acidic environment (such as the phagosome). PZA is activated by pyrazinamidase (PncA) to form pyrazinoic acid, which inactivates a vital step in fatty acid synthesis. PZA also inhibits protein translation and the ribosome-sparing process of translation by binding to ribosomal protein S1 (RpsA) in *M. tuberculosis*. Most (68-95%) PZA-resistant *M. tuberculosis* strains contain mutations in pncA or rpsA. Ethambutol (EMB) inhibits the synthesis and polymerization of cell wall arabinan, which leads to the accumulation of free mycolic acids and incomplete cell wall assembly. EMB mainly interacts with membrane-associated arabinosyltransferases encoded by three contiguous genes (embCAB operon) as an arabinose analog.<sup>7</sup> The molecular basis of resistance to EMB is not completely defined. Resistance-conferring mutations in three emb genes have been identified in *M. tuberculosis* strains.

Streptomycin (SM) is now used as a second-line drug for treating patients who have failed therapy or have MDR-TB only if the *M. tuberculosis* strain is susceptible to SM. SM inhibits protein synthesis by binding to a ribosomal protein (RpsL) and 16S rRNA. High-level resistance mainly involves missense mutations in rpsL codon 43 (rpsL43) and rpsL88, while mutations in the rrs gene cause low-level resistance. Other aminoglycosides, kanamycin (KAN) and amikacin (AMI) also inhibit protein synthesis (peptide chain elongation) in *M. tuberculosis* and are used as second-line injectable drugs for actively dividing bacteria. Resistance to KAN and

AMI is mainly associated with *rrs* mutations. Although cross-resistance between KAN and AMI has been reported, cross-resistance between SM and either KAN or AMI is not reported, hence KAN/AMI may be used for SM-resistant strains.<sup>9</sup> However, cross-resistance between KAN/AMI and other injectable agents such as capreomycin (CAP) and viomycin (VIO) (cyclic peptides) has been described. The *rrs* mutation A1401 G is associated with high-level KAN and AMI resistance but usually causes low-level resistance to CAP and no resistance to VIO while C1402 T is associated with high-level CAP and VIO resistance but usually causes low-level resistance to KAN and no resistance to AMI in *M. tuberculosis*.

The new-generation FQs (moxifloxacin, MFX and gatifloxacin, GFX) have excellent bactericidal activity against *M. tuberculosis*. The FQs inactivate DNA gyrase (composed of two A and two B subunits encoded by *gyrA* and *gyrB* genes, respectively) and inhibit DNA replication. In *M. tuberculosis*, resistance to FQs is mainly associated with mutations at codons 90, 91 and 94 of *gyrA* gene. Some FQ-resistant *M. tuberculosis* strains contain mutations at *gyrB*464 or *gyrB*495.<sup>52,4</sup>

Ethionamide (ETH), a structural analog of INH, is used as a second-line drug for MDR-TB and shares the target with INH. Similar to INH, ETH is also a pro-drug, however, it is activated by a monooxygenase (encoded by *ethA*). The *ethA* catalyses a twostep activation of ETH to its active form (4-ethyl-4-amidopyridine). Similar to INH and PZA, majority of ETH-resistant *M. Tuberculosis* strains contain mutations in *ethA* that abolish activation of prodrug. Similar to INH, the main cellular target of activated ETH is *inhA* and mutations in *inhA* regulatory region that are associated with INH resistance also cause cross-resistance to ETH.<sup>14</sup>

Kanamycin, amikacin and capreomycin are a group of amino-glycosides also known as second-line injectable drugs (SLID) used in the treatment of MDR-TB. The mechanism of SLID is that they bind to the 16S rRNA in the 30S ribosomal subunit and inhibit protein synthesis of *M. tuberculosis*. Hence, mutations in 16S rRNA (*rrs*) impart resistance to SLID. Especially a single mutation in *rrs*, A1401G is reported to explain majority of SLID resistance, viz., amikacin: 78%, capreomycin: 76%, and kanamycin: 56%. The sensitivity and specificity of GenoType MTBDRsl assay for SLID was reported to be 86.4% and 90.1% respectively. Further, additional mutations (C-14T, G-10A or G-37 T) in *eis* are also involved in resistance to kanamycin in the absence of mutations in *rrs*. Since, GenoType MTBDRsl has included the mutations from *eis* promoter region 10 to 14 (in addition to *rrs*), the sensitivity and specificity of GenoType MTBDRsl for determining kanamycin resistance alone was observed to be better than SLID as a whole (95.4% and 91.4% respectively). These results clearly indicate the need for identification of other mutations/genes involved in the resistance of SLID, thus

they can be used as molecular markers for the rapid diagnosis of SLID resistance.<sup>15</sup>

Fluoroquinolones (FLQ) (levofloxacin, moxifloxacin and ofloxacin) are used to treat MDR-TB, thus its role in the control of TB is very critical. FLQ inhibit DNA gyrase which is encoded by *gyrA* and *gyrB*. Codons 74 to 113 in *gyrA* and codons 500 to 538 in *gyrB* are known as the quinolone resistance-determining region (QRDR), and different numbering systems are used to denote the QRDR. Among mutations in *gyrA*, 81% are reported to occur in QRDR while 19% occur away from it; in *gyrB*, only 44% mutations occur within the QRDR. In *gyrA*, mutations in codon 94 explain 37% of FLQ resistance, while codons 90, 91 and 94 together explain 54% of the FLQ-resistance. The overall sensitivity and specificity of GenoType MTBDRsl assay for FQ were 93.0% and 98.3% respectively when compared to phenotypic DST.<sup>17</sup>

## CONCLUSION

The information discussed in this review helps the microbiologists and other healthcare professionals to understand the transmission and types of tuberculosis. This review also provides the new insights for the discovery of a new chemotherapy regimen for TB, either by introducing novel drugs or by modifying the existing ones.

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## REFERENCES

1. World Health Organization. Global tuberculosis report 2013. p. 1-145. Available at: [http://apps.who.int/iris/bitstream/10665/191102/1/789241565059\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/191102/1/789241565059_eng.pdf)
2. New York State Department of Health Bureau of Tuberculosis Control; 2014. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMp1402147>
3. WHO. Global Tuberculosis Control. Geneva; 2015. Available at: <https://apps.who.int/iris/handle/10665/191102>.
4. Surendra KS, Mohan A, Sharma A. Miliary tuberculosis: A new look at an old foe. *J Clin Tubercul Mycobacterial Dis.* 2016;3(5):13-27.
5. Kulchavenya E, Naber K, Bjerklund TEJ. Urogenital Tuberculosis: Classification, Diagnosis, and Treatment. *Eur Urol Suppl.* 2016;15(4):112-21.
6. Chang HC, Yu MC, Chih WL, Yu JC, Chun YC, Jui KH. Early diagnosis of spinal tuberculosis. *J Formosan Med Asso.* 2016;115(10):825-36.
7. Cary C, Jhaji M, Cincicola J, Evans R, Cheriya P, Subhash VG. A rare case of fibrostenotic endobronchial tuberculosis of trachea. *Ann Med Surg.* 2015;4(4):479-82.

8. Pravin R, Gambhire P. Abdominal Tuberculosis. *J Assoc Phys India.* 2016;64:8-47.
9. Gonzalez MJ, Jose MGG, Anibarro L, Vidal R, Esteban J, Blanquer R, et al. Consensus Document on the Diagnosis, Treatment and Prevention of Tuberculosis. *Archivos de Bronconeumologia.* 2010;46(5):255-74.
10. Richard DB. Clinical tuberculosis. *Med.* 2016;44(6):384-89.
11. Agashe V, Ganesh M, Shubhadha S, Rodrigues C. Osteoarticular tuberculosis-Diagnostic solutions in a disease endemic region. *J Infec Develop Countries.* 2009;3(7):511-6.
12. Shourya H, Rithesh KB, Baroudi K, Umar D. Tuberculous Lymphadenitis: Early Diagnosis and Intervention. *J Int Oral Health.* 2014;6(6):96-8.
13. Yencha MW, Linfesty R, Blackmon A. Laryngeal tuberculosis. *Am J Otolaryngol.* 2000;21(2):122-6.
14. Belo DSJ, Roberta FA, Elise FC, Helena DOM, Gomes DSP, Sileira DMVL. Cutaneous tuberculosis: diagnosis, histopathology and treatment - Part II. *Anais Brasileiros de Dermatologia.* 2014;89(4):545-55.
15. Musteikiene G, Miliauskas S, Sakalauskas R, Vitkauskiene A, Zemaitis M. Multidrug-resistant tuberculosis in Lithuania-Still a long way ahead. *Medicina (Kaunas).* 2016;52(2):69-78.
16. Suhail A, Mokaddas E. Current status and future trends in the diagnosis and treatment of drug-susceptible and multidrug-resistant tuberculosis. *J Infect Public Health.* 2014;7(2):75-91.
17. Soumya S, Natarajan PA, Sundaramurthi JC, Sujatha N. Recent developments in genomics, bioinformatics and drug discovery to combat emerging drug-resistant tuberculosis. *Tuberculosis (Edinburgh, Scotland)* 2016;101:31-40.

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