Review Article

Drug-resistance and its impact on cutaneous tuberculosis

Abstract

Drug resistance in tuberculosis is a universal health problem, with India and China having the highest number of multidrug resistant tuberculosis (MDR-TB) cases globally. As cutaneous tuberculosis (CTB) accounts for 1.5% of all extrapulmonary tuberculosis, drug resistance in CTB remains less discussed and understood. The sensitivity and specificity of the routine diagnostic workup for CTB are low compared to pulmonary tuberculosis. Therefore, identifying drug resistance becomes challenging and needs a high index of suspicion. Molecular techniques such as polymerase chain reaction (PCR), line probe assays, DNA microarray, and sequencing help us to identify tubercular bacilli and drug resistance early. Prompt initiation of effective therapy reduces disease-related morbidity and mortality and makes the patient non-contagious. Lately, World Health Organization (WHO) has recommended using "all oral longer MDR TB regimen" for pulmonary and extrapulmonary drug-resistant TB instead of a painful older regimen requiring long term therapy with injectables. This review focuses on the drug resistance in CTB, various methods and newer techniques to diagnose them and recent updates on treatment guidelines.

Keywords: *Cutaneous tuberculosis, drug resistance, updates*

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Introduction

The world's largest number of tuberculosis (TB) patients resides in India.[1] Approximately 26.9 lakh new cases were detected in 2019, accounting for 25% of the global caseload. India has the second largest number of patients with TB who have concomitant human immunodeficiency virus (HIV).[2] Extrapulmonary tuberculosis (EPTB) accounts for 20% of all TB cases. Cutaneous tuberculosis (CTB) accounts for 1.5% of EPTB and around 0.9% of patients attending dermatology outpatient department.[3]

Since the 1980s, the incidence of TB has been on the rise, including CTB. The reasons attributable to this increase are HIV, multidrug resistance, a surge in the use of immunosuppressive agents, increased migration with a decline in TB-control initiatives.[4] Multidrug-resistant tuberculosis (MDR-TB) is considered as resistant to both first-line drugs isoniazid and rifampicin. MDR-TB constitutes 4% of de-novo patients and 18% of formerly treated patients.[5] The prevalence of MDR-TB is increasing gradually, with India and China having the highest number of MDR-TB cases globally. WHO's Global Tuberculosis report 2020 estimates 1.71 lakh rifampicin-resistant MDR-TB cases emerging every year in the South-East Asia.[6] Most of the discussions and debates on MDR-TB appear mainly in reference to pulmonary TB and this information is not readily available to dermatologists who deal with a large number of patients with CTB. This aspect is also not well emphasized in traditional textbooks of dermatology. This prompted us to disseminate the available information on the subject.

Data about multidrug resistance in EPTB is limited. In a study from Thailand, multidrug resistance was seen in 0.5% of EPTB patients. It was also noted that drug resistance in EPTB was more often seen in patients who had coexisting pulmonary TB.[7] In a similar study from North India, multidrug resistance was seen in 13.4% of EPTB patients.[8] Direct transmission of primary resistant strain is a more significant contributor to the MDR-TB epidemic and drug resistance due to inappropriate treatment.[9] Failure to effectively control MDR-TB would result in a swift rise in the number of new drug-resistant cases and pose severe threats to TB control programs. Pre-XDR-TB (Pre-extensively

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drug resistant tuberculosis) is defined as TB with resistance to any fluoroquinolone, which includes levofloxacin (Lfx) and moxifloxacin (Mfx) in addition to resistance to both isoniazid and rifampicin. Extensively drug-resistant tuberculosis (XDR-TB) is simultaneous resistance to isoniazid (H) and rifampicin (R), as well as a fluoroquinolone and at least one of the Group A drugs.[10] As per the WHO, the prevalence of XDR-TB is 6.2% among MDR-TB cases, while in a study from India by Desai *et al*., XDR-TB constituted 6.6% of drug-resistant EPTB. However, both WHO and this large study by Desai *et al*. remain silent on drug-resistant CTB, highlighting the neglect of epidemiological data.[11,12]

Poor management of drug-sensitive pulmonary TB has led to a rise in MDR-TB which is a threat to control programs. Treating MDR-TB is challenging, costly and requires more experience and skills. It requires a further longer duration of therapy with more toxic drugs having a low success rate of treatment. It becomes challenging to control TB in areas with a higher prevalence of MDR-TB, particularly in populations affected with immunocompromized conditions such as HIV. There is poor availability of drugs for MDR TB, which needs a huge budget allocation by the governments.

With the vision to end TB as an epidemic, WHO initiated the "End TB strategy 2016–2035", which aims to bring down deaths due to TB by 95% and the number of new cases by 90%.[13] WHO defines elimination as less than one person with TB in a million population.[14] The Government of India aims to eliminate TB by the year 2025.[2]

Mechanism of drug resistance

Mechanisms such as activation of a drug efflux pump over the surface of bacteria, altered drug target and drug activating enzymes, production of drug inactivating enzymes are the common mechanisms responsible for drug resistance. They occur due to spontaneous and random mutations like insertion, deletion, and single nucleotide polymorphisms (SNPs).[15]

It can be categorized under following types:

- Natural or intrinsic drug resistance – Cell wall may act as an impermeable barrier, or bacilli may carry enzymes that degrade the drug or modify its structure to make it non-functional.
- Acquired drug resistance – It is the commonest type of drug resistance often seen in previously treated cases due to poor compliance, inadequate regimens, and reduced absorption.
- Primary drug resistance – A new case who is infected with a drug-resistant bacilli.
- Cross-resistance – Due to chemically related drugs.

Mutations in the 81 base pair region (507–533 amino acid residuals) of rpoB gene are responsible for rifampicin resistance in 97% of the cases. This region encodes for the β-subunit of the bacterial RNA polymerase. Resistance to rifampicin alone is rare. They are assumed to be resistant to other drugs as well, especially isoniazid. Thus, rifampicin resistance is regarded as an indirect hallmark for MDR-TB.[16]

Isoniazid is a prodrug. It is converted into an active form by the catalase-peroxidase (KatG) enzyme. This active isoniazid form, along with NAD, inhibits the NADH-dependent enoyl-acyl carrier protein (ACP)-reductase (InhA) enzyme, which is required for the synthesis of mycolic acid, thus inhibiting the cell wall formation. Mutations in katG, inhA, ahpC, kasA genes have been linked with isoniazid resistance. KatG mutations are most common among them and are also responsible for a severe form of resistance.[17]

Changes in the amino acids at codon 306 of the embB gene are responsible for most cases of ethambutol resistance. Mutations in the rpsL and rrs genes are responsible for resistance to streptomycin; mutations in gyrA and gyrB genes lead to fluoroquinolone resistance. Resistance to injectable aminoglycoside amikacin, kanamycin, and capreomycin is due to mutations in the rrs gene.[15] Although cases of MDR-TB without any known mutations have been seen where the mechanism of drug resistance is unclear, the detection of known mutations helps us in the early diagnosis of a substantial number of MDR-TB cases.[18]

Risk factors for MDR-TB

Default from the treatment is the most critical risk factor associated with MDR-TB. Conditions such as alcohol and substance abuse, imprisonment indirectly leads to noncompliance. MDR–TB can occur in immunocompetent patients too, while those in immunocompromized states like AIDS, uncontrolled diabetes, end-stage kidney disease, organ transplant and using immunosuppressive drugs are prone to drug resistance. Increased immigration from endemic countries with a higher prevalence of MDR-TB, crowded places with high MDR-TB cases such as healthcare facilities, prisons, homeless shelters and direct exposure to the MDR-TB positive individual are other responsible factors.[19] History of concomitant pulmonary TB and higher bacillary load due to a greater likelihood of spontaneous mutations have also been reported to lead to MDR-TB.[7,20]

MDR-TB should be suspected in patients who, despite receiving therapy, show inadequate response and clinical deterioration such as the appearance of new lesions, persistent fever, weight loss, decreased appetite, or relapse after receiving an entire course of therapy.

Clinical patterns of drug-resistant cutaneous tuberculosis

Cutaneous lesions of MDR-TB have been reported in the clinical forms of scrofuloderma, lupus vulgaris, TB cutis,

chronic non-healing ulcer, TB cutis miliaris disseminata, recurrent cutaneous abscesses, and tuberculids like erythema induratum (Bazin's disease).[21,22]

Ramesh *et al*.,[23] in a study, reported five cases of scrofuloderma in children and lupus vulgaris in a young woman having multidrug resistance. Most children had fever, weight loss, decreased appetite, and sinus formation over underlying lymph nodes. One of the children had concomitant cerebral TB. Women had an erythematous plaque over the cheek along with a few nodules and submandibular and right axillary lymphadenopathy. They all were HIV negative, suggesting cutaneous MDR-TB is not common with HIV infection as perceived.

In another study by Ramesh *et al*.[24] with three cases of cutaneous MDR-TB, an adult had a history of low-grade fever for two years presenting with cutaneous abscesses over the thigh, destruction of L4 and L5 lumbar vertebrae with local pus collection and concomitant tuberculomas in the right frontal lobe. Drug sensitivity testing showed resistance to isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin, ethionamide, and para-aminosalicylic acid (PAS). The other two were children who had an undermined ulcer over the forearm, with enlargement of draining lymph nodes. One of them had a history of fever, arthritis, and weight loss for two years, and Pott's spine destroyed the T8 thoracic vertebrae and adjacent ribs.

Goel *et al*.[25] reported a chronic non-healing painless leg ulcer over the posterior aspect of the thigh due to MDR-TB in an immunodeficient patient suffering from systemic lupus erythematosus. Tao *et al*.[26] reported a case with recurrent ulcers and erythematous plaques over the buttocks of an adult male for two years, who was previously diagnosed with pulmonary TB five years back. On tissue culture, tubercle bacilli were resistant to isoniazid, rifampicin and ethambutol. The patient had generalized malaise, dry cough and weight loss, while he had ulcers and plaque over the buttocks. A case of XDR CTB manifesting as erythema induratum (Bazin's disease) was reported by Olson *et al*.,[27] who developed multiple erythematous subcutaneous nodules over the lower limb, which eventually ulcerated. Drug sensitivity testing carried on culture from tissue samples showed resistance to multiple drugs, that is, rifampicin, isoniazid, ethambutol, streptomycin, kanamycin, and ciprofloxacin.

Investigations

Like drug-sensitive CTB, most drug-resistant CTB cases are paucibacillary, where isolation of organisms is rare. The sensitivity and specificity of all diagnostic tests are reduced; hence identifying drug resistance becomes challenging.[28] Most of the time, diagnosis relies on the clinical grounds braced with response failure to first-line antitubercular therapy. Figure 1 demonstrates the approach to a suspected case of CTB. Drug susceptibility testing (DST) is carried out to identify the drug resistance in tubercular bacilli using phenotypic and molecular tests.

Phenotypic tests – observe for growth of bacilli in the presence of antitubercular drugs.

Phenotypic DST uses culture-based processes to detect drug resistance. Solid media such as Lowenstein-Jensen is used to grow bacteria, but it takes a longer time of 3–8 weeks to produce results, while Middlebrook agar takes around 10–12 days. Liquid culture methods like BACTEC 460, Mycobacteria Growth Indicator Tube (MGIT 960) can process large samples and give results within 10 to 30 days. So liquid culture media gives faster results compared to solid culture media.[29] However, liquid culture methods require complex systems and need to be checked for the growth of non-tuberculous mycobacteria (NTM) and other contaminants not visible to naked eyes. Culture-based processes require labs with higher biosafety levels and trained persons. The sensitivity is relatively low in paucibacillary forms, which makes the demonstration of drug resistance difficult.[30]

Molecular tests – detect the genes responsible for drug resistance. The current molecular techniques used are real-time **polymerase chain reaction** (real-time PCR), Line probe assays (LPA), DNA microarray, and sequencing.

Polymerase chain reaction (PCR) technique targets either mycobacterium tuberculosis (Mtb) DNA or RNA and serves as a promising tool in diagnosing various forms of drug resistance with high sensitivity and speed. It can detect tubercle bacilli even in low concentrations (<10 organisms/ml). PCR cannot identify live and dead organisms separately, which do persist in inactive or treated cases. Therefore, they are better used for diagnostic purposes and not for monitoring.[31] The bacterial messenger RNA (mRNA) has a mean life of 3-5 min and has a higher susceptibility for damage when compared to genomic DNA; therefore, a positive mRNA signal indicates a higher possibility of viable organisms. In a study by Ramam e*t al.*, which included 28 patients with CTB, 25% tested positive for DNA PCR, while none tested positive for mRNA PCR, proving the lower sensitivity of these tests for CTB.[32]

Xpert MTB/RIF (Gene Xpert) is an automated, nested real-time PCR-based assay used to look for rpoB gene mutations. It is a closed system and uses a cartridge into which a clinical sample is inserted, thereby reducing the contamination. In 2018, Revised National Tuberculosis Control Programme (RNTCP) approved the use of chip-based "TrueNat" for point-of-care diagnosis of multidrug resistance in TB.[33] It was developed indigenously by Molbio Diagnostics India with the added advantage of being portable, battery-operated, and functional at high room temperatures.

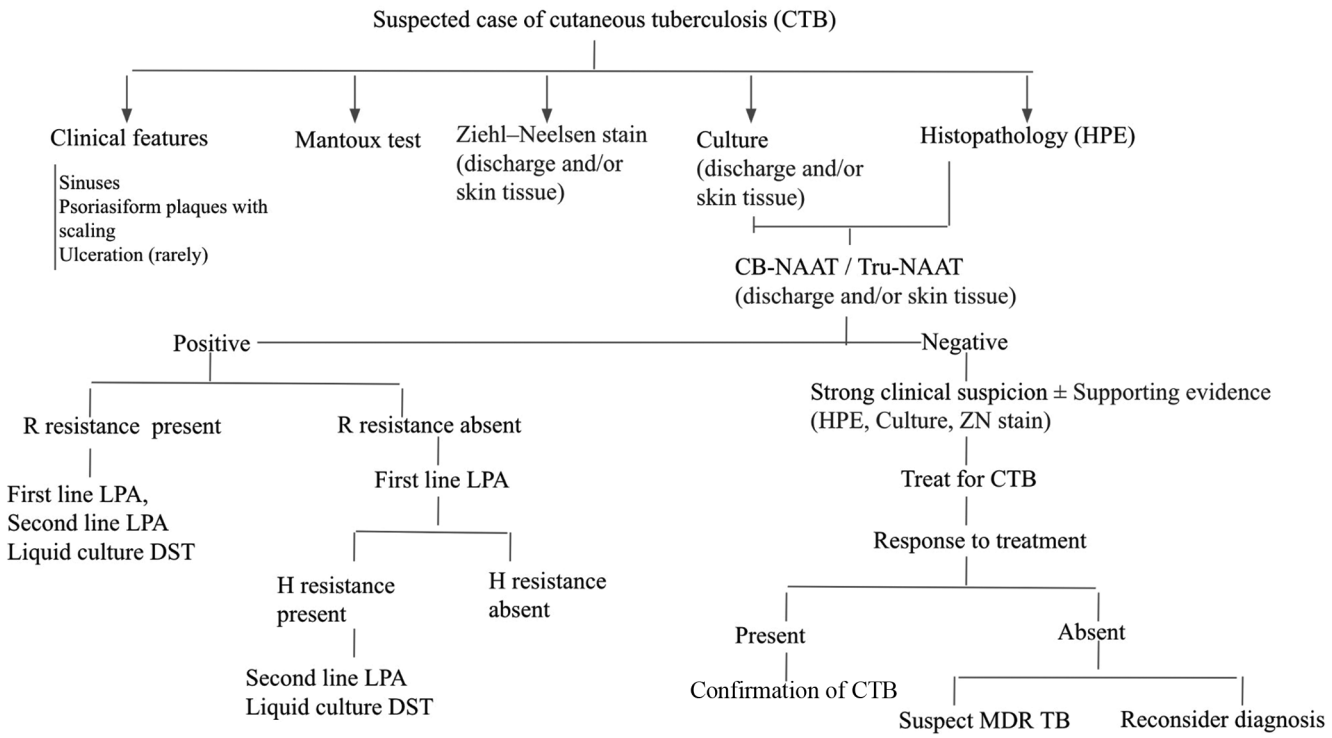

Figure 1: Approach to a suspected case of cutaneous tuberculosis with drug resistance. CB-NAAT - cartridge-based nucleic acid amplification test; R - rifampicin; H - isoniazid; LPA - Line probe assays; DST - Drug susceptibility testing; MDR-TB - Multidrug-resistant Tuberculosis

Nucleic acid amplification test

In December 2020, WHO spotlighted the latest molecular assays with newer classes of technology having higher diagnostic accuracy for TB and drug resistance. Moderate complexity automated Nucleic Acid Amplification Tests (NAATs), detects TB and drug resistance to rifampicin and isoniazid; Low complexity automated NAATs-detect resistance to isoniazid and second-line anti-tubercular drugs. High complexity hybridization-based NAATs- detects resistance to pyrazinamide.[34] Recent whole-genome sequencing (WGS) studies found that isoniazid resistance is present in almost every rifampicin-resistant case and arises ahead of rifampicin; thus, Xpert MTB/RIF (Gene Xpert) is not capable of identifying MDR-TB at early stages when only isoniazid resistance is present.[16] Evaluation for resistance to fluoroquinolone and the second-line injectable aminoglycosides is advocated whenever resistance to rifampicin is detected.[35]

Line probe assays (LPAs) use the principle of DNA–DNA hybridization, enabling them to detect multiple mutations simultaneously with the help of multiple probes. The DNA is extracted, and the target gene is amplified; these amplicons are hybridized with specifically designed complementary oligonucleotide probes causing immobilization on the surface of a strip. This complex is washed multiple times to eliminate the nonspecific binding of probes. The procedure takes around 5–7 hours, and eyes visualize the complex as colored bands on the strip.[36] Probe-based DSTs are unable to identify drug resistance if mutations occur other than the targeted genetic area. Xpert MTB/RIF (Gene Xpert) and LPAs are considered reliable proxies for MDR-TB. They can detect drug resistance in less than 2 hours with an approximate sensitivity of 95% and specificity of 98%.

Next-generation sequencing (NGS) reads the sequential genetic details of a fragment (targeted NGS) or entire genome (whole genome sequencing). This can virtually detect resistance to all the antitubercular drugs. It allows us to detect all new and old mutations, helps to predict the evolution of organisms, and identifies genotypes that predict drug-resistant phenotypes. DNA sequencing technologies are being increasingly used for patient management and drug resistance surveillance.[37]

DNA Microarray/DNA Biochip can detect numerous target genes having millions of sequences in a single run. It is being used currently for the detection of mutations causing drug resistance in MTB. Micro-arrays are minute solid support surfaces made of a substance such as glass or silicon, which acts as a platform for fixing an extensive cluster of pieces of DNA. Once the DNA is extracted, target genes are amplified using PCR and labeled with fluorescent dyes. These amplicons are now hybridized with probes to form double-stranded DNA and made immobile on the array. Immobilized hybrid DNA is washed multiple times to remove nonspecific bindings. Signal intensity from hybridized DNA is read at an appropriate wavelength under

a scanner.[38] DNA microarray may be applied directly on clinical samples to detect Drug resistant -TB but is currently not advocated by WHO.[16]

Treatment

Treatment of MDR-TB is challenging due to multiple reasons like long duration of therapy, painful nature, uncertain outcome, high cost, and severe adverse effects. With the development of therapeutically effective newer antitubercular drugs such as bedaquiline and delamanid, treatment guidelines have been modified in the recent past. WHO has a strong recommendation for use of bedaquiline in "all oral regimen" which was approved by the USFDA for TB in 2012.[39] Bedaquiline is always given under multidrug therapy and approved for regimen-based usage to avoid the development of resistance against it.[40] Another drug delamanid was approved by the European Medicine Agency (EMA) on April 28, 2014, for treatment of MDR-TB which acts by suppressing the formation of cell wall constituents, that is, methoxy mycolic acid and keto mycolic acid.[41]

WHO issued Consolidated Guidelines for the management of drug-resistant TB which emphasized the role of "Short course regimen", "Shorter all-oral bedaquiline-containing regimen", and "All oral longer MDR TB regimen". Table 1 shows the "standard drug resistant -TB" regimens.[42]

Short course regimen

Studies for a shorter course regimen were undertaken by the Damien Foundation in Bangladesh to develop an effective, safe, and inexpensive therapy for MDR-TB. The results of the sixth regimen were most successful, in which 87.9% of patients completed treatment without relapse. This regime was named the Bangladesh regimen. It had a higher cure rate and was required to be taken for a duration of nine months.[43] A similar observation was seen with the STREAM (Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB) trial, which was based on the Bangladesh regimen (but used moxifloxacin instead of gatifloxacin). WHO, reaffirmed its proposition of a short course regimen after the STREAM trial data was released.[44] WHO also emphasized preferring amikacin over kanamycin and capreomycin whenever a second line aminoglycoside is to be given.[45]

This short course regimen still had a drawback of injectables, which could be extremely painful and challenging for some individuals. The short regimen is not yet approved by WHO for extrapulmonary TB and should be avoided in patients living with HIV.[46]

Drugs used to manage cutaneous MDR-TB in the different case reports included daily injectable kanamycin with oral levofloxacin, prothionamide, cycloserine or terizidone and pyrazinamide. Kanamycin was discontinued after six months of the intensive phase. Most patients improved clinically after one to two months of therapy with resolution of fever, weight gain and simultaneous clearance of cutaneous lesions. The patients were treated for up to two years or until complete recovery.[22,23]

Shorter all-oral bedaquiline-containing regimen

The "shorter all-oral bedaquiline-containing regimen" approved by WHO in 2020 must be given for 9–12 months. Patients with fluoroquinolone resistance, severe EPTB, and those who have received any drug from the second-line tubercular drugs used in this regimen for more than a month are contraindications for this regimen. This regimen had better efficacy than the previously recommended longer MDR-TB regimens without new drugs and the injectable-containing shorter regimen.[47]

All oral longer MDR TB regimen

All MDR/RR-TB patients may be treated with longer regimens; however, the longer regimen is preferably given to those MDR/RR-TB patients who are not eligible for shorter all-oral regimens. The drugs have been recategorized to formulate the longer (18–20 month) regimen into group A, group B, and group C, based on the evidence to manage the patient and recommendations for use in DR-TB.[47] Table 2 classifies the drugs used to treat MDR-TB.

Table 1: Standard DR-TB regimen[42]

Standard DR-TB regimen		
Regimen class	**Intensive phase**	**Continuation phase**
H mono/poly DR-TB		
All oral H mono-poly DR TB regimen	(6/9) Lfx R Z E	
MDR/RR TB		
Shorter MDR TB regimen	(4-6) Mfx^h km/Am Eto Cfz Z H^h E	(5) Mfx^h Cfz Z E
Shorter all-oral bedaquiline-containing regimen	(4-6) Bdq (6) Lfx Cfz Z E H^h Eto	(5) Lfx Cfz Z E
All oral longer MDR TB regimen	(18-20) Bdq (6) Lfx Lzd Cfz Cs	

H - isoniazid; H^h - high dose isoniazid; R - rifampicin; Z - pyrazinamide; E - ethambutol; Lfx - levofloxacin; Mfx - moxifloxacin; Mfx^h - high dose moxifloxacin; km - kanamycin; Am - amikacin; Eto - etoposide; Cfz - clofazimine; Bdq - bedaquiline; Cs - cycloserine; Lzd – linezolid; DR-TB - Drug resistant tuberculosis; RR-TB - rifampicin resistant tuberculosis; MDR-TB - Multidrug-resistant tuberculosis

Table 2: Classification of drugs to treat MDR-TB[47]

Group A	Group B	Group C
Levofloxacin (Lfx) or moxifloxacin (Mfx)	Clofazimine (Cfz)	Ethambutol (E)
Bedaquiline (Bdq)	Cycloserine (Cs) or Terizidone (Trd)	Delamanid (Dlm)
Linezolid (Lzd)		Pyrazinamide (Z)
		Imipenem-cilastatin (Ipm-Cls) or meropenem (Mpm)
		Amikacin (Am) or Streptomycin (S)
		Ethionamide (Eto) or Prothionamide (Pto)
		P-aminosalicylic acid (PAS)

Group A - highly effective and strongly recommended; Group B - considered as the second alternative; Group C - used when drugs from group A or group B do not complete the regimen satisfactorily. Drugs of group C are ranked by risk-benefit ratio. Treatment starts with a minimum of four drugs which includes every drug from group A and one drug from Group B. Bedaquiline is stopped after six months of therapy, and the remaining three drugs are continued for rest of the treatment duration. When only one or two Group A drugs are used, both Group B drugs should be added. If the regimen is not completed with Group A and Group B drugs alone, Group C drugs are used to complete the regimen. Both the drugs from Group B must be used to complete the regimen in cases where any of the group A drugs are not used; Group C drugs are further added to cover the deficiency in the regimen.

WHO is against adding a single new drug to a failing regimen. Emphasis is laid on treating drug-resistant TB under the supervision and culture-based monitoring of patients on treatment. The decision on which regimen offers the best option for cure in a patient may also depend on preferences of patients and clinicians.

Immunotherapy in tuberculosis

Host immunity plays a key role in response to TB infection. Immunotherapeutic agents may enhance TB-specific immune activity, protective immunity and suppress adverse immune responses and inflammatory damage. This may help in the rapid clearance of infection, thereby reducing the duration of treatment and morbidity. A new therapeutic approach may develop in the future using these agents. Immunotherapy may have a more significant role in patients with a high risk of infections, such as people co-living with TB and HIV. Table 3 enumerates the immunotherapeutic agents, most of which are under preclinical research.[48]

Impact of COVID-19 on tuberculosis

COVID-19 pandemic and the lockdown created difficulties in providing healthcare to the masses. TB deaths increased for the first time in more than a decade during the pandemic. Notification of new TB cases in India was down by 30% in the first half of 2020 in comparison to the same time period of 2019. Globally, there was a reduction of 21% in the number of people who received care for TB in 2020 compared to 2019.[49] These undiagnosed cases will intensify the transmission chain of TB. The health infrastructure developed for COVID-19, such as GeneXpert/TrueNat and RT-PCR facilities, may be used in future to diagnose TB and drug resistance, thereby improving the peripheral reach of diagnostic facilities in TB endemic countries.

Table 3: List of immunotherapeutic agents for mycobacterium tuberculosis[48]

Immuno-active substances
Cytokines
IL-2, GM-CSF, IL-24, IL-32
Small molecule active peptides
AMPs, thymopentin
Immune blocker
IL-4
Therapeutic vaccines
Inactivated TB vaccines
M.vaccae, MIP vaccine, DAR-901 (Mk), RUTI.
TB subunit vaccines
BCG-PSN, Mtb72f/AS01E, H56: IC31, ID93/GLA-SE, AEC/BC02.
DNA vaccines
GX-70, Ag85a/b.
Chemical agents
Vitamin D, quercetin, polyvinylpyrrolidone, bergenin, allicin, ursolic acid, oleanolic acid, chicoric acid, retinoic acid, curcumin, loperamide, phosphatidylinositol mannosides.
Cellular therapy
Mesenchymal stem cells, Invariant NKT Cells, γδ T Cells, cytokine induced killer cells.

IL - Interleukin; GM-CSF - Granulocyte-macrophage colony-stimulating factor; AMPs - antimicrobial peptides; MIP - mycobacterium indicus pranii; NKT - natural killer T cells

Conclusion

Physicians must be made aware of CTB. Factors such as patient education, directly observed treatment (DOT) provider education/family involvement, quality drugs, continuous supply of drugs, appropriate dose and management of drug reaction will ensure the appropriate

treatment of the patients. Given the relative rarity of drug-resistant CTB, difficulty in isolating the bacteria from paucibacillary forms with identification of drug resistance, and lack of sufficient trials in extrapulmonary forms of MDR-TB; framing of the guideline for drug-resistant CTB with precise findings is challenging, and they should be flexible to include difficult to prove cases that do not fit into classically defined subset approach.

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Conflicts of interest

There are no conflicts of interest.

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