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A Comprehensive Literature Review of *Mycobacterium tuberculosis* Drug Resistance

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ABSTRACT

Introduction: This review examines the global challenge of antimicrobial resistance (AMR), focusing on drug-resistant tuberculosis (DR-TB) as a major contributor to the global AMR burden. It provides an overview of the increasing threat posed by DR-TB and the need for advanced detection and management strategies. **Methods:** The review synthesizes current literature on DR-TB, particularly on resistance mechanisms, diagnostic advancements, and treatment strategies. It analyzes data from recent studies on gene mutations in *Mycobacterium tuberculosis* (M.tb) and the role of the bacterial cell envelope in resistance. **Results:** Key findings include the identification of genetic mutations linked to resistance to first- and second-line anti-TB drugs. The role of M.tb's cell envelope in drug resistance and host-pathogen interactions is also highlighted. Additionally, the review presents recent advancements in diagnostic tools, emphasizing the need for universal drug susceptibility testing and shorter, all-oral treatment regimens. **Conclusion:** The review underscores the challenges in diagnosing and treating DR-TB, including the need for improved diagnostic accuracy, accessibility, and treatment adherence. It emphasizes the importance of a multi-pronged approach, incorporating healthcare system strengthening, investment in new drug research, and global collaboration to achieve TB elimination by 2030.

Keywords: drug-resistant tuberculosis, Mycobacterium tuberculosis, multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis, TB elimination

INTRODUCTION

Distribution resistance antimicrobial resistance (AMR) which is increasingly expand almost Certain will weaken provision service effective health globally , so that required multipronged approach that accelerates development antimicrobial new , and implementation life - saving treatment life This in a way more regular (Nathan, 2020). Management antibiotics that are effective in plants and animals through The One-Health approach is also becoming element important in future endeavors For combat AMR. Although bacteria resistant antibiotics and pathogens other is significant part from resistance , tuberculosis (TB) resistant drug donate global AMR burden in disproportionate amount. [1.2]

Tuberculosis resistance medicine (TB RO) still become threat in TB control and is one of the problem health public major in many countries around the world. Globally in 2019 , an estimated 3.3% of new TB patients and 17.7% of TB patients who have ever treated is resistant TB patients medicine . In 2019 , it is estimated that there are 9.96 million incidence of TB worldwide , of which 465,000 is MDR TB/RR TB. Of the estimated 465,000 RO TB patients , only 206,030 were successfully treated. found and 177,099 (86%) treated , with number success global treatment 57%. In Indonesia, the estimate of TB RO is 2.4% of all over new TB patients and 13% of TB patients who have ever treated with a total estimate incident TB RO cases of 24,000 or 8.8/100,000 population . In 2019 , around 11,500 TB RR patients were found and reported , around 48% of patients who started first line TB treatment secondly , with number success treatment 45%. [3]

Governance TB RO patients have implemented in Indonesia since 2009. TB RO treatment was established become part from the National TB Control Program with publication Regulation of the Minister of Health of the Republic of Indonesia Number 565/MENKES/PER/III/2011 concerning the National Strategy for Controlling TB in 2011-2014. National strategy in TB RO treatment always make an effort follow the latest global developments expected can give number success maximum treatment . Treatment results TB RO patients from 2009–2017 still show existence trend decline number success treatment , improvement number patient

separated treatment , and improvement number patient died . Because of that that , the Prevention Program do various breakthrough For increase coverage and quality TB RO services in Indonesia, one of which is with implementation alloy resistant TB treatment drug without injection , good alloy term short and also term long . Besides that , the Indonesian Ministry of Health has issued the Decree of the Minister of Health of the Republic of Indonesia (KMK) number 350 of 2017 concerning Appointment House Hospitals and Health Centers for do TB RO treatment and expanding availability facility service TB resistant health medicine . Improvement quality services and management TB RO patients , plus with distribution service TB RO health is expected to be evenly distributed throughout Indonesia can increase number coverage TB RO treatment and to cut off chain the spread of TB and TB RO in the community. [4]

Treatment regimen standard For tuberculosis (TB) both sensitive to drugs (DS-TB) or those that are resistant to (DR-TB) drugs have updated by WHO in May 2022. Previously , treatment for DS-TB consists of from phase intensive for 2 months with isoniazid (INH), rifampin (RIF), pyrazinamide (PZA, Z), and ethambutol (EMB, E), followed by with phase advanced for 4 months with only INH and RIF (2HRZE/4HR) (WHO, 2022b). Recommendation WHO's latest for DS-TB treatment includes implementation of a daily regimen for 4 months or more new , consisting of from rifapentine (RPT), INH, PZA, and moxifloxacin (MFX), which have been shown to No lost effective compared to DS-TB treatment regimen for 6 months. [3.5]

Recommendation WHO's latest for DR-TB treatment includes three different regimen options For patients who have diagnosed . The selection of DR-TB treatment regimen is based on various factors , including profile resistance Mycobacterium tuberculosis (M.tb) drug , history exposure to previous anti-TB drugs , as well as level severity pulmonary TB disease . Of the three available regimens , the newest and most recommended regimen For resistant TB cases rifampicin (RR-TB) or multidrug- resistant TB (MDR-TB) is combination bedaquiline (BDQ), pretomanid (Pa), linezolid (LZD), and MFX (BPaL+M),

which is a full oral regimen with duration of 6 months . For pre-XDR-TB cases , same regimen recommended but without MFX. [3.4]

Choice treatment addition for MDR/RR-TB is a 9 - month oral regimen that includes BDQ for 4–6 months combined with fluoroquinolone, ethionamide (ETH), EMB, INH doses high , PZA, and clofazimine (CFZ), as well treatment advanced for 5 months with fluoroquinolones, CFZ, EMB, and PZA. [3]

Review literature This aiming For analyze global challenges posed by resistance antimicrobial (AMR), with focus specifically for resistant tuberculosis (TB) drug as one of the contributor the biggest to Global AMR burden . Overview This explore development latest in detection and management of drug-resistant TB medication , including treatment strategies moment this and changes in definition of XDR-TB. In addition that , is needed better understanding in about similarities and/ or difference in composition sheath cells in the DR- M.tb strain as well as How change This influence interaction bacteria with cell host and results infection . In review this , we will serve information latest about change sheath cell M.tb related with resistance medicine , analyzing the impact to results infection , as well as identify gap knowledge that is still need under review more carry on.

LITERATURE REVIEW

DEFINITION

Mycobacterium tuberculosis (Mtb) resistance occurs consequence mutation spontaneously on chromosomes . Proportion bacteria Mtb that experienced mutations (wild-type resistant mutants) in patients who have not Once accept anti -tuberculosis drugs (OAT) are very small . TB treatment creates pressure selective killing bacteria MTB sensitive , while population mutant develop breed , cause resistance against OAT (resistance) obtained). [6]

In patients new , resistance OAT occurs in those who have not Once accept TB treatment or new undergo therapy not enough from One month . Infection generally obtained from individuals who have have resistant TB . While that , resistance in patients who have had treated happens to those who have accept TB treatment more from One month , including patient fail therapy , relapse , or return

after separated treatment . Resistance This can appear during therapy or consequence infection repeat from individual with resistant TB . [6]

Table 1. Categories resistance updated medicine based on definition new WHO [3]

Category Resistance Drug	Resistant to :	
Rifampicin Resistance (RR)	Rifampicin	(+)
	Isoniazid	(-)
	Levofloxacin or Moxifloxacin	(-)
	Bedaquilina or Linezolid	(-)
Multi Drug-Resistant (MDR)	Rifampicin	(+)
	Isoniazid	(+)
	Levofloxacin or Moxifloxacin	(-)
	Bedaquilina or Linezolid	(-)
Pre-Extensively Drug-Resistant (Pre-XDR)	Rifampicin	(+)
	Isoniazid (Possibly	+)
	Levofloxacin or Moxifloxacin	(+)
	Bedaquilina or Linezolid	(-)
Extensively Drug-Resistant (XDR)	Rifampicin	(+)
	Isoniazid (Possibly	+)
	Levofloxacin or Moxifloxacin	(+)
	Bedaquilina or Linezolid	(+)

Information :

(+) show resistance

(-) show sensitivity

Minimum against One fluoroquinolone drugs .

** Minimum against One " Group A" drugs (WHO).*

Factor Causes of Resistant TB Drug

Resistance against OAT in general caused by improper treatment adequate or No in accordance Standard . Factors the causes include: [7]

a. **Health workers**

Diagnosis that is not appropriate

Treatment No use the appropriate regimen

Dosage , type , amount , and duration treatment No adequate

Lack of education to patient

b. **Patients**

No comply recommendation medical

No discipline in consuming OAT

Stop treatment in a way unilateral

Experience disturbance absorption drug

c. **TB Control Program**

Limited availability of OAT

Low quality of OAT

DRUG RESISTANCE MECHANISM IN *MYCOBACTERIUM TUBERCULOSIS*

Rifampicin

Rifampicin is derivative rifamycins were introduced in 1972 as agent antituberculosis . This is one of the most effective anti-TB antibiotic and, together with isoniazid, to become base in regimen multi- drug therapy for TB. Rifampin active against the basil that is grow or not grow (metabolism) slow). Mechanism Work rifampin in *M. tuberculosis* is with binds to the β subunit of RNA polymerase , so that hinder elongation of messenger RNA. Most of isolate clinical *M. tuberculosis* is resistant to rifampicin own mutations in the *rpoB gene* that encodes the β subunit of RNA polymerase . Mutations This cause change conformation that reduces affinity to medicine , so that causing resistance. [8]

About 96% of isolates *M. tuberculosis* is resistant to rifampicin own mutations in the 81 bp long "hot-spot region" that includes codons 507–533 of the

rpoB gene . Mutations in codons 516, 526, and 531 are the most frequent. associated with resistance rifampicin in part big research . Although more rarely , few the report also noted existence mutations outside the "hot-spot region" of *rpoB* . Resistance cross with other rifamycins may occurred . Mutations in some codons (e.g. , 518 or 529) are associated with resistance level low to rifampin , but Still prone to to other rifamycins such as rifabutin or rifalazil . This important for TB patients who need antiretroviral therapy , because rifabutin has effect more induction low to enzyme cytochrome P450 CYP3A oxidase. [8]

Resistance monotherapy to rifampin is very rare , and almost all resistant strains to rifampicin is also resistant to drug others , especially isoniazid. Therefore that , resistance rifampicin often used as marker replacement for MDR-TB. Study sequencing genome latest find existence mutation compensation in *rpoA* and *rpoC* , which encode the α and β' subunits of RNA polymerase , in resistant *M. tuberculosis* strains to rifampicin with mutations in *rpoB* . Mutations compensation This allegedly return fitness strain inside body human and associated with improvement ability transmission in a number of condition . [8]

Isoniazid

Isoniazid was introduced in 1952 as anti-TB agents and remains become base joint TB treatment rifampicin . Different with rifampicin , isoniazid only active against the basil that is replicate in a way metabolic . Also known as isonicotinic acid hydrazide, isoniazid is a pro-drug that requires activation by enzymes catalase / peroxidase KatG , encoded by the *katG gene* , for produce its effects . Isoniazid works with hinder synthesis sour mycolic via NADH-dependent enoyl-acyl carrier protein (ACP)-reductase, encoded by *inhA* . [8]

Two mechanisms main isoniazid resistance associated with *katG* and *inhA* gene mutations or its promoter region . The most common mutations is S315T on *katG* , which causes deficiency isoniazid products in forming the necessary isoniazid-NAD adduct For activity antimicrobial . Mutation This associated with resistance level high (MIC > 1 µg/mL) to isoniazid and more often found in MDR strains. Mutations second most common occurs in the *inhA promoter region* , which causes overexpression Inha or mutations in its active site , so that reduce affinity

against isoniazid-NAD adducts. Mutations in *inhA* No only cause resistance to isoniazid but also to ethionamide, which has the same target . [8]

Studies latest show that the 4R isomer of the isoniazid-NADP adduct can hinder dihydrofolate reductase (*DfrA*) in *M. tuberculosis* , indicating possibility involvement mutation *dfrA* in isoniazid resistance . Some study find polymorphism nucleotide single in another gene in isolate clinical *M. tuberculosis* is resistant to isoniazid, including *cash* and area intergenic *oxyR-ahpC* as well as *furA-katG* . However , the role directly as reason isoniazid resistance has not been fully proven . [8]

Ethambutol

Ethambutol first introduced in TB treatment in 1966 and is part from regimen line First moment this . Ethambutol nature bacteriostatic against the growing basil breed with bother biosynthesis arabinogalactan in the cell wall . In *M. tuberculosis* , the *embCAB gene* is composed of as an operon encodes enzyme arabinosyl transferase which plays a role in synthesis arabinogalactan .

Mechanism resistance to ethambutol associated with mutations in the *embB gene* , with mutation in position *embB306* as the most common found in Lots research . However , some the study also found mutation in *embB306* in isolates that are still prone to to ethambutol . Study latest show that mutation in *embB306* No always related with resistance to ethambutol , but with trend For develop resistance to more Lots medicine . [8]

Pyrazinamide

Pyrazinamide introduced in TB treatment in the early 1950s and today become part from regimen line First standard . Pyrazinamide is analog nicotinamide at work with inhibits semi- dormant bacilli in environment sour like TB lesions . Pyrazinamide is a pro-drug that needs to be converted become form active , acid pyrazinoate , by the enzyme pyrazinamidase / nicotinamidease encoded by the pncA *gene* . [8]

Mechanism Work pyrazinamide involving conversion pyrazinamide become sour pyrazinoate , which interferes with energy membrane bacteria and inhibit membrane transport . Study latest show that sour pyrazinoate can also

inhibits fatty acid synthase type I in replicating TB bacilli . In addition there it is hypothesis new that sour pyrazinoate inhibiting the trans- translation process in *M. tuberculosis* , but proof more carry on Still required . Mutation in the *pncA* gene still become most common findings in resistant strains to pyrazinamide , although a number of studies report resistant strains without mutation *pncA* , which indicates possibility the presence of other regulatory genes that have not been identified . [8]

Streptomycin

Streptomycin is antibiotics first used in a way success fighting TB, isolated from microorganisms land *Streptomyces griseus* . Unfortunately , resistance against him quick appear Because used as monotherapy . Streptomycin is active aminoglycoside against the basil that is grow and work with hinder initiation translation in protein synthesis . Resistance to streptomycin especially associated with mutations in the *rpsL gene* which encodes the ribosomal protein S12, and the *rrs* gene which encodes the 16S ribosomal RNA. In addition that is , a mutation in the *gidB gene* , which encodes enzyme 7-methylguanosine methyltransferase (m7G), has been associated with resistance level low to streptomycin . Although streptomycin No Again part from regimen line First standard , understanding about mechanism its resistance still important in more TB therapy complex . [8]

Fluoroquinolone

Fluoroquinolone moment This used as drug line second in resistant TB treatment (MDR-TB) drugs . Ciprofloxacin and ofloxacin are derivative synthetic from compound parent sour nalidixate , which was found as product side from chloroquine antimalarial. Fluoroquinolone generation new such as moxifloxacin and gatifloxacin currently evaluated in clinical trials and proposed as antibiotics line First For shorten duration TB treatment . [8]

Fluoroquinolone Work with inhibits topoisomerase II (DNA gyrase) and topoisomerase IV, two enzymes important for continuity life bacteria . In *Mycobacterium tuberculosis* , only topoisomerase II (DNA gyrase) is present and is the primary target fluoroquinolones . Topoisomerase II is a tetramer consisting of of two subunits α and β, encoded by the genes *gyrA* and *gyrB* , which catalyze DNA supercoiling .

Mechanism main resistance fluoroquinolones in *M. tuberculosis* is mutation chromosomes in the area determinant resistance quinolones (*quinolone resistance-determining region* , QRDR) of *gyrA* or *gyrB* . The most common mutation occurs at positions 90 and 94 of *gyrA* , but mutations at positions 74, 88, and 91 have also been reported . A review systematic latest has published about mutation related gyrase with resistance fluoroquinolones in *M. tuberculosis* . [8]

One of findings interest in *M. tuberculosis* is existence polymorphism naturally at position 95 in *gyrA* which is not related with resistance fluoroquinolones , because they are also found in strains that are still prone to to fluoroquinolones . Another study showed that mutation simultaneous *T80A* and *A90G* in *gyrA* cause hypersensitivity to a number of quinolones , which show that problem resistance fluoroquinolones in *M. tuberculosis* Possible more complex than expected previously . [8]

Resistance cross between fluoroquinolone generally assumed happened , even though There is report that some resistant strains to gatifloxacin and moxifloxacin still prone to to ofloxacin. Mechanism efflux is also suspected play a role in resistance fluoroquinolones in *M. tuberculosis* . [8]

Kanamycin , Capreomycin , Amikacin , Viomycin

Fourth antibiotics This own mechanism same action in hinder protein synthesis . Kanamycin and amikacin including group aminoglycosides , whereas capreomycin and viomycin is antibiotics peptide cyclic . All drug This is line both used in MDR-TB management . [8]

Kanamycin and amikacin hinder protein synthesis with change structure *16S rRNA* . The most common mutations in resistant strains to kanamycin occurs at positions 1400 and 1401 of the *rrs* gene , which causes resistance level tall to kanamycin and amikacin . However , mutations at position 1483 have also been reported . [8]

Resistance cross full between kanamycin and amikacin No always happen as before allegedly . Some studies show levels and patterns varying resistance , indicating that other mechanisms may be involved . Besides that , resistance level low to kanamycin has associated with mutations in the promoter region of the *eis*

gene , which encodes enzyme aminoglycoside acetyltransferase . Mutations at positions −10 and −35 of the *eis* promoter cause improvement protein expression and resistance level low to kanamycin , but No to amikacin . [8]

Capreomycin and viomycin own structure similar and binding ribosomes in the same location , between the small and large subunits . Both show resistance cross full as reported in studies previously . Mutations in the *tlyA gene* , which encodes *rRNA methyltransferase* , also associated with resistance to capreomycin and viomycin . [8]

Ethionamide

Ethionamide is derivative from sour isonicotinate which is structural similar with isoniazid. Drugs This is a pro-drug that requires activation by monooxygenase encoded by the *ethA gene* . Ethionamide bother synthesis sour mycolic with to form stir with NAD inhibiting enzyme *enoyl-ACP reductase* . Resistance to ethionamide happen consequence mutations in *ethA* , *ethR* , and *inhA* . In addition that is , a mutation in *mshA* , which encodes enzyme important For biosynthesis mycothiol , has also been associated with resistance to isoniazid and ethionamide . [8]

Para- Aminosalicylic Acid (PAS)

PAS is one of the the first anti - TB drug used in treatment together with isoniazid and streptomycin . When this , PAS is considered as drug line second in MDR-TB treatment . Mechanism PAS work is believed similar with para-aminobenzoic acid (PABA), which competes with enzyme *dihydropteroate synthase* , so that bother synthesis folate . Mutations in *the thyA* and *folC genes* , which encode enzyme *dihydrofolate synthase* , has identified as reason PAS resistance in isolates clinical *M. tuberculosis* . [8]

Cycloserine

Cycloserine is first line anti-TB drugs both of which work as analog *d-alanine* , which inhibits activity *d- alanine:d -alanine ligase* and synthesis peptidoglycan . Cycloserine can also hinder *d-alanine racemase (AlrA)* is required For conversion *l-alanine* become *d-alanine* . [8]

Thioacetazone

Thioacetazone is old drugs used in TB treatment because its beneficial in vitro activity to *M. tuberculosis* and its very low cost . However , the drug This own problem toxicity , especially in HIV -infected patients . The drug This including in WHO group 5 and work with hinder synthesis sour mycolic . [8]

Macrolides

Macrolides more often recommended For treatment infection other mycobacteria because his limited activities to *M. tuberculosis* . Clarithromycin including in WHO group 5. Resistance intrinsic to macrolide associated with permeability wall low cell and expression *emr37* , which encodes methylase on *23S rRNA* , so that hinder binding antibiotics . [8]

Clofazimine

Clofazimine is compound riminophenazine reported own anti-TB activity for a long time. Because of the existence of other more effective anti-TB drugs effective as well as effect side like pigmentation skin , its use more Lots limited to the treatment of leprosy. [8]

Linezolid

Linezolid is antibiotics group permitted oxazolidinones For treatment infection skin and nosocomial pneumonia consequence Gram- positive bacteria . Drugs This Work with hinder protein synthesis on the 50S ribosomal subunit . Resistance against linezolid still seldom found in *M. tuberculosis* , but has reported that mutations in *23S rRNA* and the *rplC* gene contribute to resistance . Mechanism efflux is also suspected play a role in resistance *M. tuberculosis* to linezolid. [8]

Table 2. First-line TB drugs first and second , the genes involved in activation , and the me involved. [8]

Drug	Gene	Mechanism Involved
Isoniazid	*katG , inhA*	Catalase/peroxidase; enoyl reductase
Rifampicin	*rpoB*	RNA polymerase
Pyrazinamide	*pncA , rpsA*	Pyrazinamide ; ribosomal protein 1
Ethambutol	*embB*	Arabinosyl transferase

Table 2. First-line TB drugs first and second , the genes involved in activation , and the me involved. [8]

Drug	Gene	Mechanism Involved
Streptomycin	*rpsL , rrs , gidB*	S12 ribosomal protein, 16A rRNA, 7-methylguanosine methyltransferase
Quinolones	*gyrA , gyrB*	DNA gyrase
Capreomycin	*rrs , tlyA*	16S rRNA, rRNA methyltransferase
Kanamycin/Amikacin	*rrs*	16S rRNA
Ethionamide	*ethA*	Enoyl-ACP reductase
Para- aminosalicylic acid	*thyA , folC*	Thymidylate synthase A

Table 3. Mechanism Work anti-TB drugs . [8]

Drug	Target	Mechanism Work Drug
DNA/RNA/Protein Synthesis		
Rifampicin	Hinder *Mycobacterium tuberculosis* DNA-dependent RNA polymerase For press RNA synthesis	Tuberculosis sensitive drug
Rifapentine	Hinder *Mycobacterium tuberculosis* DNA-dependent RNA polymerase For press RNA synthesis (similar with rifampicin); has time beak longer , concentration minimal inhibition more low , and protein binding is higher tall compared to rifampicin	Tuberculosis sensitive drug
Moxifloxacin	Inhibits topoisomerase II (*DNA gyrase*) *of Mycobacterium tuberculosis*	Tuberculosis sensitive drug or tuberculosis resistant rifampicin / multi drug
Linezolid	Prevent formation complex initiation bacterial 70S ribosome functions For hinder bacterial protein translation	Tuberculosis resistant rifampicin / multi drug or tuberculosis pre-extensive resistant drug
Permeability Wall Cell		
Isoniazid	Hinder enzyme *Inha* in a way competitive through formation covalent isoniazid-nicotinamide admixture adenine dinucleotide For prevent biosynthesis sour mycolic	Tuberculosis sensitive drug

Table 3. Mechanism Work anti-TB drugs . [8]

Drug	Target	Mechanism Work Drug
Pyrazinamide	Sour pyrazinoate (form active pyrazinamide) inhibits synthesis fatty acids with bother enzyme synthase fatty acid I, inhibits ATP production , and inhibits *Mycobacterium tuberculosis* protein synthesis	Tuberculosis sensitive drug
Ethambutol	Hinder arabinosyltransferase *Mycobacterium tuberculosis* For bother biosynthesis component wall cells containing arabinose and prevent division bacteria	Tuberculosis sensitive drug
Pretomanid	Hinder biosynthesis sour mycolic in condition aerobic ; causes poisoning respiration in *Mycobacterium tuberculosis* through effect nitrosylation from nitroimidazole that releases pre-reactive nitrogen species in condition anaerobic	Tuberculosis resistant rifampicin / multi drug or tuberculosis pre-extensive resistant drug
Ethionamide	Hinder enzyme *Inha* in a way competitive (similar with isoniazid) via formation covalent stir ethionamide-nicotinamide adenine dinucleotide For prevent biosynthesis sour mycolic	Tuberculosis resistant rifampicin / multi drug
Delamanid	Hinder synthesis methoxy - and keto-mycolates through system coenzyme *F420* as well as produces nitrogen oxide through effect nitrosylation from nitroimidazol	Tuberculosis resistant rifampicin / multi drug

Production Energy

Table 3. Mechanism Work anti-TB drugs . [8]

Drug	Target	Mechanism Work Drug
Bedaquilina	Hinder ATP synthase activity mycobacterial	Tuberculosis resistant rifampicin / multi drug or tuberculosis pre-extensive resistant drug
Clofazimine	Bother potassium absorption and ATP production with interact with phospholipids membrane *Mycobacterium tuberculosis* , causes destabilization membrane	Tuberculosis resistant rifampicin / multi drug

Note : Longer treatment regimens for tuberculosis resistant drug can use combination customized medication based on results previously , intolerance to drug certain , or a diagnosis of tuberculosis extensive resistant drug

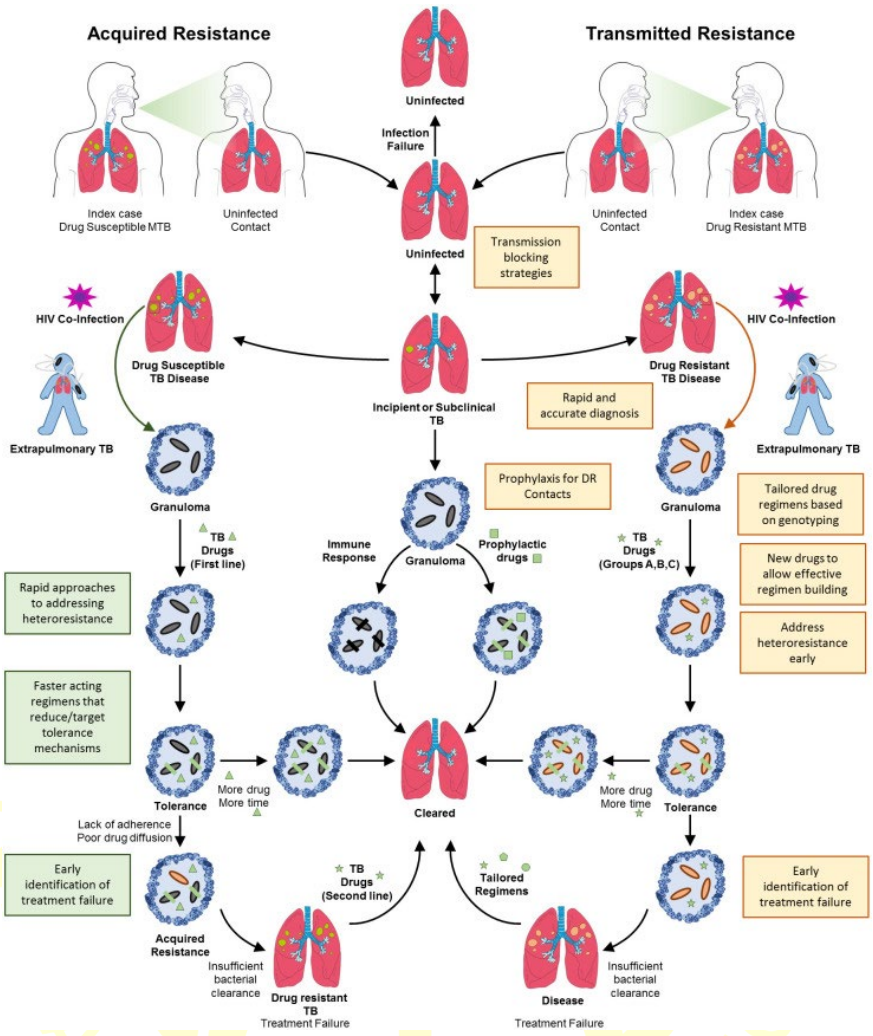


Figure 1. Transmission Mechanism [8]

Sheath Cell M.tb

Sheath cell *Mycobacterium tuberculosis* (M.tb) is structure thick and complex that delivers protection unique for bacteria in various environments. [9] Sheath This consists of from a number of layers each of which contributes to its complex composition . Layers deepest is similar plasma membrane with Lots species bacteria others . Outside plasma membrane , there is layer peptidoglycan (PG) bound in a way covalent with polysaccharide arabinogalactan (AG). Non-reducing end from AG experienced esterification with sour mycolic chain unique length (C60-C90) for *Mycobacterium* spp. and forms the core of the cell wall . [9,10]

Lipidoglycans , glycolipids , and bound lipids non - covalently across MAcs and create peripheral lipid layer . Above peripheral lipid layer This there is material outside in the form of " capsule " consisting of of α- glucan , arabinomannan , mannan, and several other proteins . The peripheral lipid layer covers the major known lipid classes influence results infections , such as *phthiocerol dimycoserosates* (PDIMs), phenolics glycolipids (*PGLs* , present in some strains *of M.tb*), trehalose monomycolate (*TMM*) and dimycolate (*TDM*), diacyl / triacyl / pentaacyl-trehalose (*DAT/TAT/PAT*), sulfolipid (*SL-1*), and phosphatidyl -myo-inositol mannosides (*PIMs*) and their lipidoglycans such as lipomannan (*LM*) and *mannose-capped lipoarabinomannan* (*ManLAM*) (Figure 2). [9,10]

Importance peripheral lipid layer confirmed by the facts that component This covers 40% of overall sheath cell *M.tb* (Garcia- Vilanova et al., 2019). Sheath cell M.tb is components that continue evolve and adapt and very important For protect bacteria from condition adverse environment during infection . Many anti-TB drugs such as isoniazid (INH) and ethambutol (EMB) target biosynthesis sheath cell For destroy barrier this and weaken bacteria . Anti-TB drugs that target sheath cell nature bactericide , allowing other drugs for penetrate deeper . [10,11]

The important thing is , a lot mutations that cause resistance to anti-TB drugs emerge in track biosynthesis sheath cells , so that development new anti-TB drugs become very important For oppose improvement resistant TB cases (DR-TB) drugs that have recently This happened . In whole , sheath cell *M.tb* own Lots layer different that works protect bacteria in various environment as well as give resistance to Lots different drugs . [11,12]

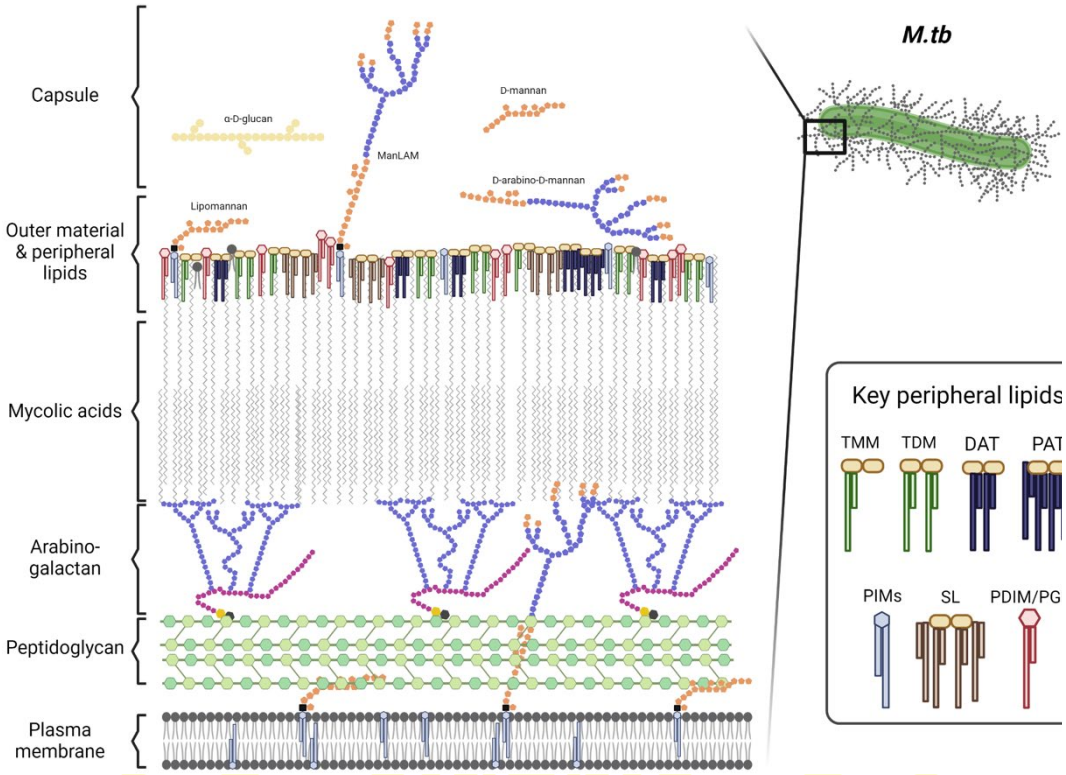


Figure 1. Mycobacterium tuberculosis cell envelope . Adapted from Mary Jackson (Jackson, 2014). TMM, trehalose monomycolate ; TDM, trehalose dimycolate ; DAT, diacyltrehalose ; PAT, pentaacyl-trehalose ; PIMs, phosphatidyl -myo-inositol mannoside ; SL, sulfolipids ; PDIM, phthioserol dimycoserose ; and PGL, glycolipids phenolic . Size cell envelope components No depicted in scale proportional .

Target Sheath Cell M.tb for Anti-TB Drugs

Understand sheath cell *M.tb* is very important For recognize complexity regimen necessary anti-TB treatment For kills sensitive *M.tb* strains to drugs (DS-TB) and those that are resistant drugs (DR-TB).

In the 2HRZE/4HR regimen , INH is the prodrug that activates at first involving reduction M.tb ferric catalase-peroxidase *KatG* by hydrazine For forming ferrous KatG . Then , ferrous KatG react with oxygen to form oxyferrus KatG activates INH (Wang et al., 1998) . After activated , INH inhibits *InhA* , enoyl reductase *M.tb* , with to form stir covalent with coenzyme NAD. This INH-NAD

adduct act as a competitive inhibitor *InhA* in action slow and strong For bother Macs biosynthesis . [9,12]

Rifampin (RIF) inhibits DNA- dependent RNA polymerase , so press RNA synthesis and causes death bacteria). Pyrazinamide (PZA) diffuses to in *M.tb* active expressing enzyme pyrazinamidase , which converts PZA to form active sour pyrazinoate . Compound This hinder synthesis essential fatty acids For bacterial growth and replication . [9]

EMB in general direct hinder *M.tb arabinosyltransferases* (EmbA , EmbB , and EmbC), interfere with biosynthesis component arabinose from sheath cell M.tb such as AG and LAM as well prevent division bacteria . EMB is believed to impact large in structure and permeability sheath cell because the arabinan AG domain maintains Macs barrier.9

On recommendation WHO's latest for DS-TB treatment for 4 months with rifapentine (RPT), INH, PZA, and moxifloxacin (MFX), substitution of RIF with RPT provides profit because RPT has concentration minimum inhibitory concentration (MIC) more low , time beak more length , and affinity more protein binding high , so that produce therapy more short with toxicity lower . [9,10]

For DR-TB, the regimen latest oral treatment is BPaL + MFX for MDR/RR-TB or BPaL just for pre-XDR TB. Effects combination drug This to sheath cell Not yet fully understood . However , bedaquiline (BDQ) inhibits ATP synthase. important mycobacteria For production energy in *M.tuberculosis* . [13] Pretomanid (Pa) inhibits biosynthesis MAcs and causes poisoning respiration *M.tb* through effect nitrosylation its nitroimidazole , which releases reactive nitrogen species in condition anaerobic . [9,10]

In general overall , all regimen anti-TB treatment developed For increase permeability sheath cell *M.tb* , disturbing production energy , as well as hinder synthesis of DNA, RNA, and protein (Table 3). The combination drug in regimen This increase permeability sheath cell *M.tb* while in a way simultaneous targeting critical processes For continuity his life . This is also necessary For prevent emergence resistance medicine and shortening duration treatment .

PRINCIPLES OF DRUG SUSCEPTIBILITY TESTING DIAGNOSIS

In accordance with recommendation World Health Organization (WHO), rapid diagnosis tuberculosis (TB) and testing vulnerability Drug Susceptibility Testing (DST) should be universally done in a way systematically in every individuals who demonstrate symptom clinical TB. Profile resistance need confirmation TB bacteriology , followed by with detection resistance drug use method phenotypic (culture or phage based) which observes growth mycobacteria in media containing drug or method genotypic (based on molecular or sequencing) which detects known genes contribute to drug resistance . [4]

Testing vulnerability drug to available anti-TB drugs are essential because :[4]

- Help in election the right therapy .
- Useful For confirm emergence resistance medication , especially in patients who fail therapy .
- Used For surveillance of resistant TB (DR-TB) drugs at the health program level .

Unfortunately , no all DST tools available in a way wide For use clinical , especially in countries with high TB burden that has source Power limited . Therefore Therefore , the selection of DR-TB diagnostic strategies must be consider epidemiology disease local , relevance information diagnostic For taking decision clinical , availability option therapy , as well as feasibility , cost , accuracy , and time processing in system existing health . [4]

Testing Vulnerability Drug in a way Phenotypic (pDST)

In high-income countries low and intermediate (LMICs), microscopy of resistant bacilli acid (AFB) still become method main in the diagnosis of TB. However , the method This own sensitivity low (60%) and requires 5,000 to 10,000 bacilli per mL of specimen For detecting Mycobacterium tuberculosis (MTB) in stock coloring , as well as No can detect DR-TB. Pure culture mycobacteria , good solid media based and also liquid , fixed become standard gold For MTB detection and DST testing . [4]

Phenotypic DST testing use concentration critical (Critical Concentrations/CC), namely concentration drug lowest that can be hinder growth of 99% of the wild MTB population . In addition that , WHO has also establish clinical breakpoints (CB) for a number of medicine , namely concentrations above CC that distinguish susceptible strains from the resistant ones . If MTB growth occurs above CB , then organism the possibility big No will respond medicine at the dose standard , and in a number of case , medicine the can used in higher doses tall For reach effectiveness . [4]

In 2018 , WHO published guide regarding the CC that has been established and of a nature temporary for DST against all drug in groups A, B, and C. For isoniazid (INH) and moxifloxacin (MFX), WHO has designated CB for resistance level low and high , namely : [3.4]

- INH: 0.1 mg/L (resistance low) and 0.4 mg/L (resistance high) in MGIT.
- MFX: 0.25 mg/L (resistance low) and 1.0 mg/L (resistance tall).

However , testing resistance to one CC or CB point possible No Enough For guide optimal therapy . Although method measurement Concentration Minimum Inhibitory Concentration (MIC) can give profile more resistance complete , method This No used routinely . [4]

Solid Culture Method

WHO recommends two types of solid media main For MTB isolation and testing its vulnerability to anti-TB drugs , namely : [4]

Media based egg (Lowenstein–Jensen/LJ).

-based media (Middlebrook 7H10 and 7H11).

A number of DST method based on solid culture used For Detecting DR-TB includes :

a) Method Proportion

Method This done with inoculating LJ media containing CC from certain anti-TB drugs (test media) and media without drug (control media) with MTB culture suspension . Resistance results determined based on comparison amount colonies in media containing drug to control media : [4]

- If ≥1% of the MTB population is resistant , the results reported as " resistant ".
- If <1% of the MTB population is resistant , the results reported as " vulnerable ".

Method This validated For part big drug line first and second TB. However , the method This not ideal for testing resistance to pyrazinamide (PZA) because requires a low pH that is not can maintained in media. [4]

b) Method Absolute Concentration

Method This use inoculum standard from MTB isolates on media with various concentration medicine , and results resistance stated as MIC, namely concentration drug lowest that inhibits MTB growth (<20 colonies). If resistance reported at an MIC above the specified CC or CB , then drug the No may used without consultation expert . [4]

c) Method Ratio Resistance

Method This comparing the MIC of the test isolate with the MIC of a reference MTB strain (e.g. , strain H37Rv). The results categorized as : [4]

- Prone to full (ratio ≤2).
- Resistant high (ratio ≥8).
- Method dense culture based own a number of limitations , including :
- Need 3–6 weeks time For get results .
- Need infrastructure complex laboratory .
- Own cost around 22 USD per test .

Liquid Culture Method

Common liquid media used For MTB growth includes Middlebrook 7H9 broth, which was used in automated culture methods (e.g. , BACTEC MGIT, VersaTREK , MB/ BacT ALERT) or manual method (Sensitizer). Advantages of liquid culture compared to solid culture includes : [4]

- **More sensitive** : Has a limit of detection (LoD) of up to 10 bacteria per mL, compared to 100 bacteria per mL in solid culture .
- **More fast** : Can give results in time 4–24 days with MGIT 960.

- **Automation** : Required A little manual intervention and use system fluorescence For detect MTB growth .

One of the most common system used is **BACTEC MGIT** , which offers testing resistance to drug line first and second TB, including PZA, fluoroquinolone (FQ), bedaquiline , and linezolid. Detection time varies from about 10 days For smear sample- positive up to 2–6 weeks For smear- negative sample , with average time is about 23 days . [4]

However , the liquid culture method also has a number of limitations , such as :

- More prone to to contamination compared to solid culture .
- Cost more high (~29 USD per test , including DST).
- Need training laboratory special For interpretation results .

Although liquid culture method more fast and sensitive , its use Still confined to the laboratory center Because cost height and needs infrastructure special . Therefore that , in many countries with high TB burden , combination various methods , including microscopy , culture, and methods molecular , fixed required For monitoring response patient to TB treatment . [4]

Vulnerability Testing Drug with Observation Microscopic (MODS)

MODS is a liquid culture- based test that detects MTB and assesses vulnerability direct anti-TB drugs from sample sputum or MTB isolates . Methods This utilise more MTB growth fast in liquid media and appearance microscopic typical . Sample inoculated to in a 24-well microtiter plate containing Middlebrook 7H9 media, then observed with microscope light upside down . Microcolony detected in an average of 7 days For smear- positive sample , more fast than solid culture method . Agreement between MODS and standard culture methods is 97% for RIF, 95% for INH, and 98% for RIF/INH. MODS is recommended by WHO for testing direct sample phlegm and valid for susceptibility testing drug line first and second . However , MODS requires skills microscopy upside down and material finished use special , and supervision daily after day fifth incubation . MODS biosafety risk is equivalent with conventional culture , so that need action level two

prevention . MODS fits For laboratory reference , but Not yet recommended For laboratory level low . [4]

Reductase Test Nitrate (NRA)

NRA detects MTB's ability to reduce nitrate become nitrite , which was identified use Griess reagent . This test can done directly on the sample sputum smear- positive or MTB isolates . The sensitivity of NRA for INH, RIF, EMB, and STR was 96%, 97%, 90%, and 82%, respectively , with specificity 99%, 100%, 98%, and 96%. Result time varies from 5-28 days for NRA direct and 5-14 days For No direct . NRA based liquid offer time results more fast (7 days) with accuracy tall for RIF, INH, OFL, AMK, KAN, and CAP. However , NRA has not validated For new anti-TB drugs . [4]

Microtiter Test (REMA)

REMA measures viability MTB cells with blue resazurin reduction become red resorufin young . This test can detect vulnerability drug line first and second with results easy read through change color . REMA shows agreement tall with reductase test nitrate and standard culture methods . However , validation for EMB, STR, and new anti-TB drugs Still required . [4]

Phage Test

Phage test using bacteriophages that infect MTB to detection fast and vulnerability testing drugs . Reporter phages such as LRP can detect MTB within 48 hours in culture isolates . Its sensitivity was 95.9% for smear- positive samples and 88.89% for smear- negative . However , this test not enough effective on load bacteria low (<10,000 CFU/mL). Commercial kits like FASTPlaqueTB -RIF and Actiphage has available , but its use in samples direct Still in development . [4]

Vulnerability Testing Drug Genotypic (gDST)

WHO recommends molecular testing fast For detect resistance anti-TB drugs such as RIF, INH, and FQ. Several tests can detect resistance against RIF and

INH, while other covers drug line second . However , the gDST test For drug new like bedaquiline and pretomanide Still limited Because lack of concordance data genotypic-phenotypic . [4]

Probe Based Test

- **GenoType MTBDRplus and MTBDRsl** : Detect mutations in *the rpoB* , *katG* , and *inhA genes* for RIF and INH, as well as *the gyrA* , *embB* , and *rrs* genes for FQ and injection . Its sensitivity varies from 96% for RIF to 44% for KAN.
- **Genoscholar** : Detecting MTB and mutations resistance against RIF, INH, PZA, FQ, and KAM. Sensitivity for RIF and INH were 98.9% and 90.6%, respectively.
- **GeneXpert MTB/RIF and Ultra** : Detects MTB and RIF resistance within 2 hours. Xpert Ultra is faster sensitive (88%) than Xpert RIF (72%).
- **Abbott RealTime MTB RIF/INH** : Detects MTB, RIF, and INH with sensitivity 96% and specificity 97%.
- **FluoroType MTBDR** : Detects MTB, RIF, and INH with sensitivity 97% for RIF and 70-92% for INH.
- **BD MAX MDR-TB** : Detects MTB, RIF, and INH with sensitivity of 90.6% for MTB and 82% for INH.
- **Cobas MTB RIF/INH** : Detects mutations in *rpoB* , *katG* , and *inhA* with sensitivity of 97.2% for RIF and 96.9% for INH.
- **Based Isothermal Amplification (LAMP)**
  LAMP is a method fast For detect MTB and RIF/INH resistance in time not enough from one hour. The sensitivity was 93.1% for INH and 89.1% for RIF. Suitable For area limited source Power .
- **Micro PCR Test Chip Based (Truenat MTB-RIF-Dx)**
  Truenat detect MTB and RIF resistance in time not enough from one hour. Its sensitivity and specificity comparable with Xpert MTB/RIF.

Test Based Sequencing

- **Deeplex MYC-TB** : Detects resistance against 15 anti-TB drugs with sensitivity 95% and specificity 97%.
- **Sequencing Generation Following (NGS)** : Offers approach comprehensive For detect mutation resistance . Its sensitivity is 100% for INH, RIF, and FQ, but more low for PZA (29.4%).

Spectrometry (MALDI-TOF-MS)

MALDI-TOF-MS detects heavy protein molecules or oligonucleotide related resistance . Method This promising For identification fast MTB and resistance medicine . [4]

Comparison of Phenotypic , Genotypic , and Sequencing Tests

Genotypic testing and sequencing as Xpert, LPA, and WGS show agreement tall with phenotypic testing (pDST). WGS has agreement highest (93%) and can detect heteroresistance . However , pDST Still required For detect mutation new and resistance below detection limit sequencing . Second method This each other complete in the diagnosis and treatment of DR-TB. [4]

DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS ACCORDING TO THE MINISTRY OF HEALTH OF THE REPUBLIC OF INDONESIA

Type Inspection Microbiology for TB RO

A number of inspection laboratory microbiology used For establish diagnosis and monitor drug -resistant TB treatment drugs (TB RO), including : [4]

a. **Test Fast Molecular (TCM)**

Inspection use tool Xpert MTB/RIF is method amplification sour nucleic automatic detecting *Mycobacterium tuberculosis* complex as well as resistance to rifampicin (rpoB gene). The results can obtained in about 2 hours with category as following :

- *M. tuberculosis* detected with results resistance rifampicin :
- "Rif Res" (Resistance)
- "Rif Sen" (No Resistance)

- "Rif Indet " (Indeterminate)
- *M. tuberculosis* No detected (" Negative ")
- Failed result (invalid, no result, or error)

b. **Inspection Microscopic**

BTA examination with Ziehl- Neelsen staining done as part from sensitivity test after patient confirmed TB Rifampicin Resistance , before start TB RO therapy . In addition that , examination this is also done in monitoring treatment in accordance schedule . The result categorized as positive (scanty, 1+, 2+, 3+) or negative .

c. **Inspection Culture**

Method This used For grow and identify *M. tuberculosis* using solid media (Lowenstein-Jensen/LJ) or liquid (Mycobacteria Growth Indicator Tube/MGIT). Solid media more cheap but need time 3-8 weeks , while liquid media more fast (1-2 weeks) but more expensive. The result in the form of positive (with or without gradation) or negative .

d. **Sensitivity Test Phenotypic**

This test aiming For know resistance *M. tuberculosis* to anti-TB drugs (OAT) with method phenotypic (LJ or MGIT media). Examination This only can conducted in the laboratory certified by Laboratory National TB Reference Capacity laboratory for culture and sensitivity testing Keep going developed For increase inspection to drug new ones recommended by WHO (2018), such as bedaquiline , linezolid, clofazimine , delamanid , and pyrazinamide .

In 2019, the TB line susceptibility test examination one and two switch to Standardized Drug Susceptibility Test Packages (SDP) system . SDP panel includes various anti-TB drugs with laboratory references that perform sensitivity tests on solid media and also liquid .

e. **Second Line LPA Inspection**

The Line Probe Assay (LPA) method is used For detect resistance to rifampicin (rpoB), isoniazid (inhA , katG), and drug group fluoroquinolones (gyrA , gyrB) and drugs TB line injection second (eis , rrs). When This TB program in Indonesia only using LPA line secondly , with results that can be achieved obtained in 48 hours time . Examination done 1-2 times per week For efficiency , with a turn-around time (TAT) of around 2-5 days Work .

LPA results can be in the form of :

M. tuberculosis detected / not detected detected

Sensitive / resistant to fluoroquinolones (levofloxacin , moxifloxacin dose low and high)

Sensitive / resistant to drug injection line second (kanamycin , amikacin , capreomycin)

TB RO Diagnosis Flow

Diagnosis of RO TB confirmed through sensitivity testing *M. tuberculosis* use method phenotypic or genotypic . According to Minister of Health Regulation No. 67 of 2016, TB diagnosis is carried out with TCM or inspection microscopic . [4]

For TCM examination , two specimens are required sputum quality good (mucopurulent , volume 3-5 ml). Sputum can collected with method In the morning, in the morning , or Occasionally , with a minimum interval of 2 hours between taking . One of the sample checked with TCM, while others are kept For repetition If the result is indeterminate, invalid, error, no result, or If Rif Res results were found in patients with risk low TB RO. [4]

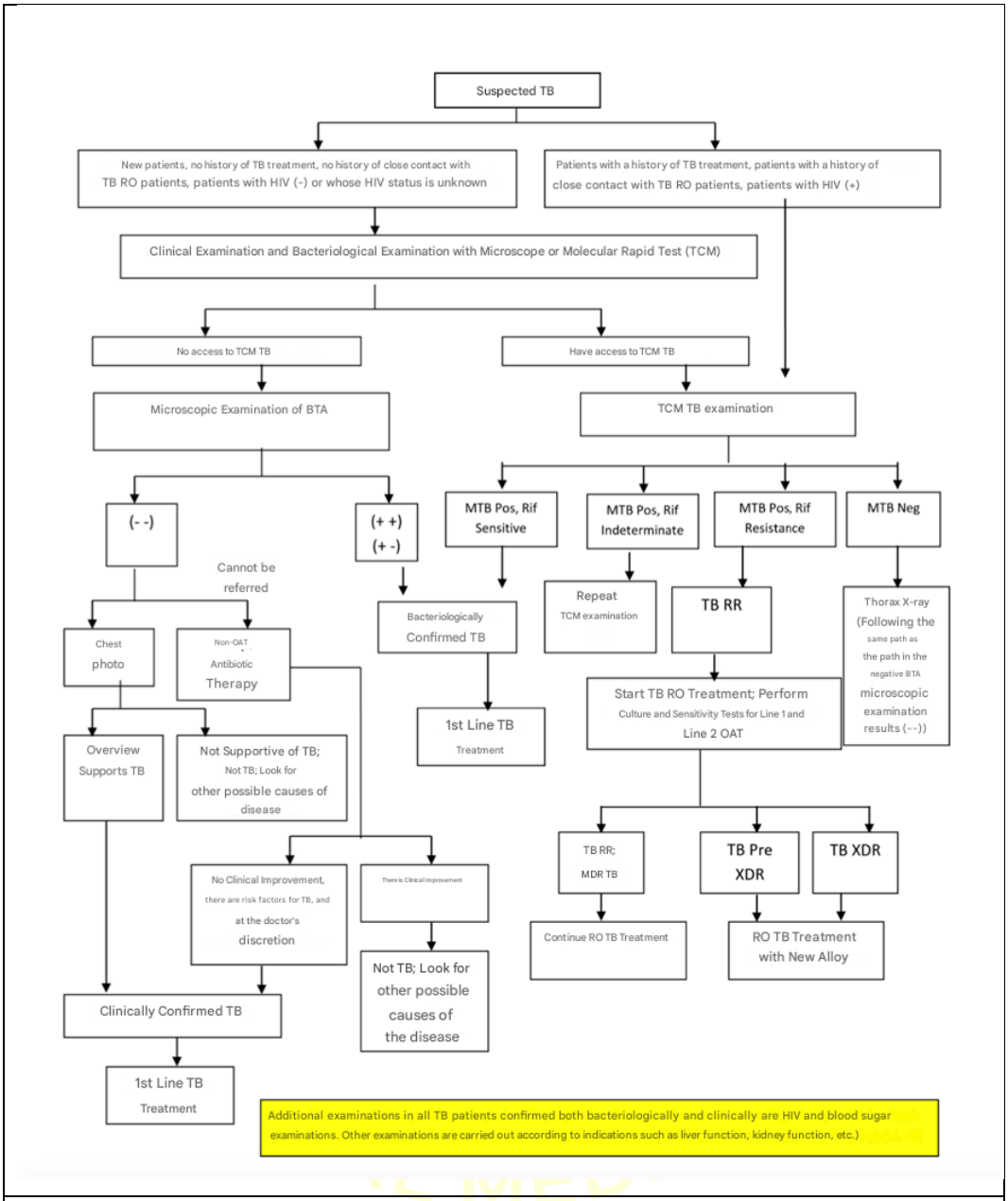
Based on factor risk , patient categorized as at risk tall or low against TB RO. If the patient with risk low get Rif Res results , then TCM examination must repeated use specimen sputum second in the facility service same health . Repetition only done one time, with possibility results advanced in accordance with findings laboratory . [4]

Patient with TCM results show *M. tuberculosis* resistance rifampicin from group risk low TB RO needed undergo inspection repeat use specimen sputum second in the facility service health with TCM access . Repetition This only done once , with possibility results as following : if results second still show resistance rifampicin , patient confirmed as TB RO; if the result sensitive rifampicin , patient stated as non- resistant TB ; and if the result negative , indeterminate, error, invalid, or no result, then patient considered as TB sensitive Because originate from group risk low . [4]

In TB RO handling , laboratory culture and sensitivity testing own role important , with guarantee quality conducted by the Laboratory National Reference (LRN) BBLK Surabaya. Examination of sensitivity test can done with method fast or conventional , which is ideal capable detect resistance to rifampin and isoniazid in patients new , and resistance to fluoroquinolones in patients with history treatment previously . If the TCM results show resistance rifampicin , examination more carry on with LPA line two carried out For detect resistance to fluoroquinolones and drugs injection line two, with expected results go out in seven day . [4]

Availability sensitivity test results to every drug should No hinder giving therapy for patient with condition threaten soul . However , the risk addition resistance consequence therapy that does not in accordance still need be noted . If the results of the sensitivity test to first line anti-TB drugs second Not yet available , decision therapy based on history treatment , pattern resistance case index , as well as surveillance data sensitivity drug latest . TB RO management requires access fast to inspection diagnostics and sensitivity testing For ensure the right therapy since beginning treatment . WHO through the End TB strategy *2015–2030* emphasize the importance of early diagnosis and universal susceptibility testing for all TB patients , with inspection molecular fast recommended For all individual with TB symptoms , as well as sensitivity tests rifampicin for patients who have confirmed bacteriological . [4]

In a number of case , result TCM examination and sensitivity test phenotypic can show results that are not appropriate (discordant). If TCM shows *M. tuberculosis* positive but culture negative , decision therapy based on TCM results and analysis clinical patient , with consider possibility error laboratory or condition specimen . On the other hand , if TCM is negative but culture positive , decision treatment referring to the results culture as standard TB diagnosis gold . If there is difference between TCM results and sensitivity test rifampicin , evaluation more carry on required For determine decision the right therapy , with consider possibility mutation specific or error laboratory . [4]



Drug -Resistant TB Diagnosis Flow [4]

Treatment Strategy Tuberculosis Resistance Drugs (TB RO)

Treatment of resistant TB (TB RO) medicine aims For ensure that patient with resistant TB rifampicin (RR TB) or multidrug-resistant TB (MDR-TB) receive fast , appropriate therapy standard , and quality high . Therapy regimen consists of from combination anti -tuberculosis drugs (OAT) first line first and line second , which is customized with sensitivity test results to *Mycobacterium tuberculosis* .

Decisions related to change of therapy regimen created by team expert experienced clinician in handling TB RO. [4]

Before start treatment , patient must undergo inspection the beginning that includes evaluation organ functions such as kidneys , liver , and heart , as well as inspection level electrolytes and laboratory parameters others . During the therapy period , monitoring strict required For evaluate response treatment as well as detect effect possible side arise . Evaluation post-treatment is also important use ensure success therapy and prevention relapse disease . [4]

For increase effectiveness therapy , TB RO treatment must be started in time maximum seven day after the diagnosis is confirmed . The patient generally undergo therapy take care road with supervision direct from Supervisor Swallowing Drugs (PMO). According to recommendation WHO's latest 2020 , Indonesia has adopt a regimen without drug injection , which consists of of two types therapy , namely a long-term regimen short with duration of 9–11 months and long-term regimen long with duration 18–24 months . [4]

Grouping TB RO Drugs and Treatment Flow

Based on WHO recommendations 2018, the National TB Control Program has renew classification drugs used in TB RO therapy . Medicines This grouped become three group main : [4]

- **Group A** : Levofloxacin / Moxifloxacin , Bedaquiline , Linezolid
- **Group B** : Clofazimine, Cycloserine / Terizidone
- **Group C** : Ethambutol , Delamanid , Pyrazinamide , Imipenem- cilastatin , Meropenem, Amikacin / Streptomycin , Ethionamide / Protionamide , p-aminosalicylic acid

TB RO therapy process begins with inspection Test Fast Molecular (TCM). If the results show existence resistance to rifampicin , then specimen patient sent For sensitivity test examination medicine (LPA line) second and culture). Therapy can started quick after LPA results available or in time seven day If results Not yet out . [4]

Patients who meet the requirements condition can given a long-term regimen short , while those who don't fulfil criteria will undergo therapy with long term regimen long . Some criteria patients who can receive a long-term regimen short covering No existence resistance to fluoroquinolones , no own history contact with pre-XDR/XDR TB patients , not yet Once receive OAT line second during One month or more , and No currently in condition pregnant , breastfeeding , or experiencing pulmonary / extrapulmonary TB heavy . Besides that , HIV patients or child age above six year can also under consideration for this regimen . [4]

Treatment of RO TB with Long-Term Regimen Short

Long term regimen short consists of from seven type medicine in phase beginning , which then reduced become four medicine in phase continued . Bedaquiline given during six month first , regardless from duration phase beginning . In overall , treatment This in progress for 9–11 months , with phase beginning range between 4–6 months and phase advanced for 5 months . [4]

During the therapy period , the patient must undergo routine monitoring that includes inspection clinical , evaluation microbiology (BTA and culture), as well as inspection laboratory like function liver , kidneys , electrolytes , and electrocardiography (ECG). If in the month fourth results BTA examination still positive , then the LPA line second and sensitivity test repeat must done For determine step next . [4]

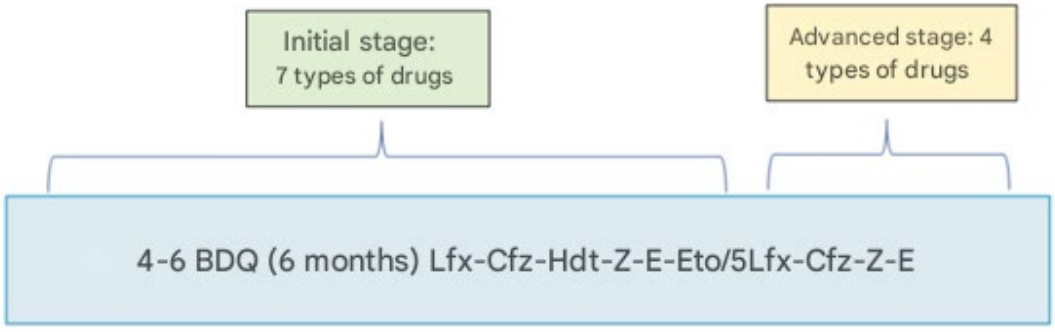


Table 4. Duration Giving Drugs in Short-Term TB RO Treatment Combination [4]

No	Drug Name	Stage (4-6 months)	Stage Continued (5 months)	Total Duration Giving
1	Bedaquiline (Bdq)*	V	-	6 months (without notice duration stage beginning)
2	Levofloxacin or Moxifloxacin	V	V	9-11 months
3	Clofazimine	V	V	9-11 months
4	Ethionamide	V	-	4-6 months
5	INH dosage tall	V	-	4-6 months
6	Pyrazinamide	V	V	9-11 months
7	Ethambutol	V	V	9-11 months

Table 5. OAT Dosage Based on Body Weight For Short-Term TB RO Treatment Combination [4]

Drug Name	Dose Drug Daily	Packaging	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
Bedaquiline *	100 mg tablets	-	4 tabs (2 weeks) first), 2 tabs Monday /Wednesday/ Friday (22 weeks)	-	-	-	-
Levofloxacin	500 mg tablets	-	1.5	2	3	4	4
Moxifloxacin (dosage) standard)	400 mg tablets	-	1	1.5	1.5	1.5	1.5
Moxifloxacin (dosage) tall)	400 mg tablets	-	1 or 1.5	1.5 or 2	2	2	2
Clofazimine	50 mg cap	-	2	2	2	2	2
	100 mg cap	-	1	1	1	1	1
Ethambutol	15–25 mg/kg	400 mg tablets	2	2	3	3	3
Pyrazinamide	20–30 mg/kg	400 mg tablets	3	4	4	4	5
	500 mg tablets	-	2	3	3	3	4
Ethionamide	15–20 mg/kg	250 mg tablets	2	2	3	3	4

Table 5. OAT Dosage Based on Body Weight For Short-Term TB RO Treatment Combination [4]

Drug Name	Dose Drug Daily	Packaging	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
INH (dose tall)	10–15 mg/kg	300 mg tablets	1.5	1.5	2	2	2

Notes :

- *Bedaquiline* consumed 2 × 2 tablets @100 mg each day (morning and night) for 2 weeks first , then 1 × 2 tablets @100 mg 3 times a week for 22 weeks next .
- Ethambutol and Pyrazinamide Dosage customized based on weight in specified range .

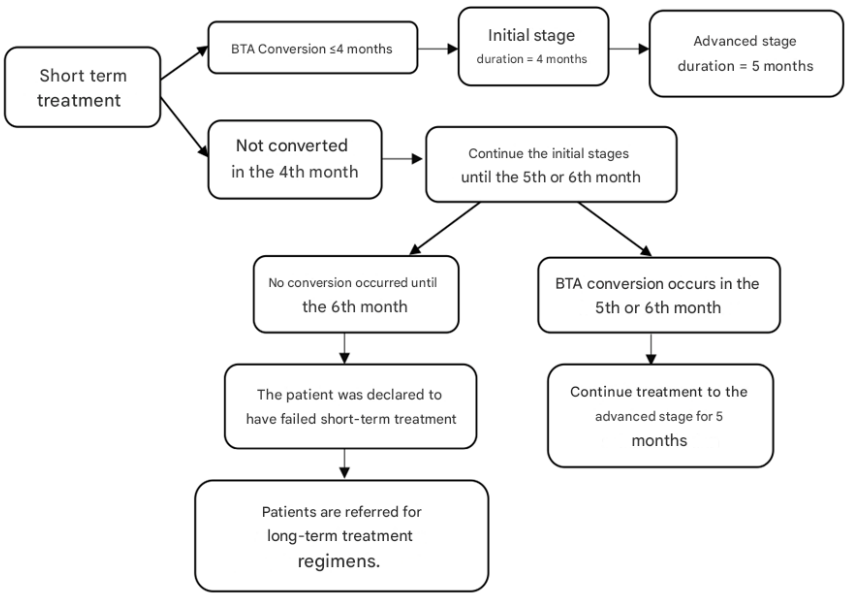


Figure 4. Scheme for administering short -term RO TB treatment combinations [4]

Treatment of RO TB with Long- Term Regimen

Patients who do not fulfil condition for long term regimen short will get therapy with long term regimen long lasting for 18–24 months . Selection drug in this regimen depends on the pattern resistance bacteria and conditions patient clinical . [4]

In long term regimen preparation long , at least five effective drugs must used . Medicine main chosen from Group A, then added from Group B and Group C for complete combination therapy . After bedaquiline stopped after six month use , therapy still must contains at least three effective medicine to stay optimal in eradicate *Mycobacterium tuberculosis* is resistant. [4]

Example alloy long-term TB RO treatment long without injections that can be given: [4]

Table 6. Example of Long-Term TB RO Treatment Combination based on Patient Condition [4]

No	Condition or Resistance Pattern Patient	Amount Drugs that are CONTRA-INDICATED	Amount Drugs that CAN BE ADDED	Examples of Treatment Combinations Long Term Achievable Given
1	RR/MDR TB patients who do not can STR	No There is	Group A: 3 Group B: 2 Group C: No need	**6 months :** Bdq – Lfx – Lzd – Cfz – Cs **14 months :** Lfx – Lzd – Cfz – Cs
2	Resistance / contraindications Bdq	1 medicine Group A (Bdq)	Group A: 2 Group B: 2 Group C: 1	Lfx or Mfx – Lzd – Cfz – Cs – E (or other drugs from Group C)
3	FQ resistance (pre-XDR TB) or FQ contraindications	1 medicine Group A (FQ)	Group A: 2 Group B: 2 Group C: 1	**6 months :** Bdq – Lzd – Cfz – Cs – E **14 months :** Lzd – Cfz –

Table 6. Example of Long-Term TB RO Treatment Combination based on Patient Condition [4]

No	Condition or Resistance Pattern Patient	Amount Drugs that are CONTRA-INDICATED	Amount Drugs that CAN BE ADDED	Examples of Treatment Combinations Long Term Achievable Given
				Cs – Z (or other drugs from Group C)
4	Resistance / contraindications Lzd	1 medicine Group A (Lzd)	Group A: 2 Group B: 2 Group C: 1	**6 months :** Bdq – Lfx – Cfz – Cs – E **14 months :** Lfx – Cfz – Cs – Z (or other drugs from Group C)
5	Resistance / contraindications Bdq and FQ	2 drugs Group A	Group A: 1 Group B: 2 Group C: 2	**20 months :** Lzd – Cfz – Cs – Dlm (6 months) – E (or other drugs from Group C)
6	Resistance / contraindications Bdq and Lzd	2 drugs Group A	Group A: 1 Group B: 2 Group C: 2	**20 months :** Lfx or Mfx – Cfz – Cs – In (6 months) – Z (or other drugs from Group C)
7	FQ and LZD resistance / contraindications	2 drugs Group A	Group A: 1 Group B: 2 Group C: 2	**6 months :** Bdq – Cfz – Cs – E – Z **14 months :** Cfz – Cs – E – Z (or other drugs from Group C)
8	Failed RR/MDR TB patients STR treatment	2 drugs Group A, B	Group A: 1 Group B: 1 Group C: ≥3	**20 months :** Lzd – Cs – Dlm – Z – E – PAS or combination drug Other

Table 6. Example of Long-Term TB RO Treatment Combination based on Patient Condition [4]

No	Condition or Resistance Pattern Patient	Amount Drugs that are CONTRA-INDICATED	Amount Drugs that CAN BE ADDED	Examples of Treatment Combinations Long Term Achievable Given
				Group C as appropriate condition patient
9	Resistant / intolerant to Cfz or Cs	1 medicine Group B (Cfz or Cs)	Group A: 3 Group B: 1 Group C: 1	**6 months :** Bdq – Lfx – Lzd – Cfz or Cs – Z **14 months :** Lfx – Lzd – Cfz or Cs – Z
10	Resistant / intolerant to Cfz and Cs	All (2) drugs Group B	Group A: 3 Group B: 0 Group C: 2	**6 months :** Bdq – Lfx – Lzd – Dlm – Eto **14 months :** Lfx – Lzd – Eto
11	Resistance / contraindications Bdq (A) and Cfz (B)	1 medicine Group A, B	Group A: 2 Group B: 1 Group C: 2	**6 months :** Lfx or Mfx – Lzd – Cs – Dlm – E **14 months :** Lfx or Mfx – Lzd – Cs – E
12	FQ (A) and Cs (B) resistance / contraindications	1 medicine Group A, B	Group A: 2 Group B: 1 Group C: 2	**6 months :** Bdq – Lzd – Cfz – Eto – Z **14 months :** Lzd – Cfz – Eto – Z
13	Resistance / contraindications Bdq (A), Cfz , and Cs	1 medicine Group A, 2 drugs Group B	Group A: 2 Group B: 0 Group C: ≥3	**6 months :** Lfx or Mfx – Lzd – Dlm – Z – Eto **14 months :** Lfx or Mfx – Lzd – Z – Eto

Table 6. Example of Long-Term TB RO Treatment Combination based on Patient Condition [4]

No	Condition or Resistance Pattern Patient	Amount Drugs that are CONTRA-INDICATED	Amount Drugs that CAN BE ADDED	Examples of Treatment Combinations Long Term Achievable Given
14	Resistance contraindications Lzd (A), Cfz , and Cs	/ 1 medicine Group A, 2 drugs Group B	Group A: 2 Group B: 0 Group C: ≥3	**6 months :** Bdq – Lfx or Mfx – Dlm – Z – E – Eto **14 months :** Lfx or Mfx – Z – E – Eto

Notes :

- Example alloy in table Not yet covers all regimen options .
- Election drug Group C adjusted with condition patient , considering order effectiveness drug .
- **Lfx more recommended** compared to Mfx For reduce risk QT interval prolongation .
- On giving **Bdq , Pyrazinamide (Z) can added** Because results studies show effect synergistic .

6 Bdq - Lfx or Mfx – Lzd – Cfz - Cs / 14 Lfx or Mfx- Lzd – Cfz - Cs

Monitoring and Evaluation

During the therapy period , the patient must undergo monitoring tight which includes evaluation clinical , examination microbiology , and examination laboratory Periodic . Evaluation post- treatment done every six month for two years For ensure No There is recurrence . If there is signs relapse or failure therapy , patient must quick checked more carry on For determine the appropriate treatment strategy . [4]

Decentralization TB RO Treatment

For increase access patient to treatment , decentralization program applied , where patients who have stable can continue therapy in the facility primary health

, such as health center closest or facility service health satellite . Decentralization process This involving coordination between service health , home Sick referrals , and health centers For ensure continuity treatment without reduce effectiveness therapy monitoring . [4]

Dosage and Preparation Drug

Dose drug in an adjusted RO TB regimen based on patient 's weight . Each drug own range the dose that must be taken into account with careful For ensure its effectiveness at a time reduce risk effect dangerous side effects . Table dose for long term regimen short and long available in guidelines national TB RO. [4]

Initiation and Evaluation Treatment

Treatment for RO TB is not must wait all results inspection beginning For started . If the condition patient urgent , therapy can quick given based on TCM results and analysis clinical . Patients who require maintenance more intensive will referred to to House Sick TB RO referral , and after the condition stable , treatment can continued at the facility nearest primary health care . [4]

Evaluation Post Treatment

After finish treatment , patient still must monitored in a way periodic For ensure No There is recurrence . Evaluation post-therapy done every six month for two years with examination that includes anamnesis, examination physical , BTA, culture , and photos thorax . Besides that , the patient is also given education about Behavior Life Clean and Healthy (PHBS) for prevent risk the occurrence infection repeat or relapse . [4]

With comprehensive strategy implementation this , it is expected TB RO treatment can become more effective , safe , and can accessible to all patients , including in areas with source Power limited health . [4]

CONCLUSION

Tuberculosis resistance (DR-TB) medication remains become threat big for global health , especially with increasing MDR-TB and XDR-TB cases . M. tuberculosis resistance occurs consequence mutation genetics that appear from treatment that is not adequate , causing difficulty in TB control . Progress

diagnostics , such as Xpert MTB/RIF, Line Probe Assay (LPA), and Next-Generation Sequencing (NGS), have allow detection resistance more medicine fast and accurate . However , the limitations access in low-income countries low Still become obstacle main in implementation detection early and appropriate therapy .

Treatment strategies now switch to a long-term oral regimen shorter the more effective and can increase compliance patients , such as combination bedaquiline , linezolid, and fluoroquinolones. However , the challenges main covering limitations diagnostics , costs high , and compliance low therapy , which can contribute to the emergence of more strains resistance . For to overcome DR-TB, it is necessary approach comprehensive which includes strengthening system health , investment in research and development drug new , and improvement global collaboration . With steps this , the global community can move more near towards the target of TB elimination by 2030 .

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