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Recent Trendsin Treatment of Multidrug Resistant In Tuberculosis

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ABSTRACTS:
Drug resistance is reduction in effectiveness of an anti-microbial agents used in inhibiting the microorganisms orcuring a disease. Mycobacterium tuberculosis is responsible for causing tuberculosis can acquire multiple drugresistance by not responding to Isoniazid and Rifampicin the two most powerful anti-TB agents. The complications ofdrugresistanceinTBelevatesduetosomeoftheriskfactorslikeinadequatetreatmentcompliance,non-complianceofthe patientsto the treatment.

Proper diagnosis of the disease and switching to modified drug therapy may improve the treatment outcome. Thedrug treatment involves usage of combination of drugs Isoniazid, Rifampicin, Ethambutol along with other anti-microbialagents,andnutritionaltherapy,immunotherapy.Inthisreviewwediscussedabouttheoccurrence,treatmentofmultidrugresistancetuberculosisalongwith drugsundertrialsandnutritionalrequirements.

Keywords: Multidrugresistanttuberculosis;Mycobacteriumtuberculosis;Non-compliance;Nutritionaltherapy;Immunotherapy.

I. INTRODUCTION

Tuberculosis(TB)isaninfectiousdiseasecausedbyMycobacteriumspecies(M.tuberculosisinhumansandM.bovisincattle).Themortalityrateishighfortuberculosisnext toAIDS.Researchesshowedthatapproximatelyaboutmorethanonebilliondeathsoccurredduetotuberculosis around the world till now. TB is progressive and spreadsthroughtherespiratorytractasanasaldelivery. Thedevelopmentofthediseasefrominitialinfectiontoactiveprimary tuberculosis occurs within 1-3 years. The development ofresistanceismulti-facetedandisinfluencedbysomeofthefactorslikesocio-economic,pathologicalandenvironmentalconditions [1,2].

Epidemiology
In India, the incidence of multi drug resistant tuberculosis is 3.4%(or) less. Of these, Rifampicin resistance accounts for about 1% or less[3].

Multidrug-resistanttuberculosis(MDR-TB)
ItisaconditioninwhichmycobacteriumtuberculidevelopsresistancetoIsoniazidandRifampicin,thetwomosteffectivefirstlineanti-TBmedicines.PatientswithMultiDrug-ResistantTuberculosis(MDR-TB) require treatment with second-line treatment regimens,which are more complex than those used to treat patients withoutdrug-resistant TB [4].

ExtensivelyDrug-ResistantTB(XDR-TB)isaconditioninwhichMycobacterium tuberculi responds only to few second-line anti-TBmedicines[5].

Drugresistance
Drugresistanceisreductionineffectivenessofamedicationsuchasan antimicrobial inkilling a microbeor condition.

Naturalresistance
Somemicrobeshavealwaysbeenresistanttocertainanti-microbialagent.Theyaredevoidofthemetabolicprocessorthetargetsitewhichisaffectedbytheparticulardrug.Eg:Gramnegativebacilliarenormally unaffected by Penicillin G and M. tuberculosis is insensitivetotetracyclines

Acquiredresistance
It is the development of resistance by an organism (which wassensitivebefore)duetotheuseofanAMAoveraperiodoftime.

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Pathogenesis

Most bacilli of mycobacterium undergo frequent mutations andthus exhibit resistance to drugs, thus requiring usage of multiple drugregimens. The mutation rates for different drugs are as included inTable1.

Drug	AverageMutationRate
Isoniazid	2.56×10^{-8}
Rifampicin	2.25×10^{-10}
Ethambutol	1×10^{-7}
Streptomycin	2.95×10^{-8}
Pyrazinamide	1×10^{-3}

Table1:Mutationratesofselecteddrugs.

In the treatment using a first line drug, the number of TB bacilli isdecreased due to the action of drug in killing the organisms. Eventhough, some of the organisms survive and become drug resistantmutants.

Themultiplicationofthesemutantsgradually leadstoproductionofsufficient number of bacilli enough for reappearance of symptoms.Thisistermed"thefallandrisephenomenon ".Resistanceisproducedautomaticallyforeveryantitu berculardrugeachatonetimegradually.The main aim of modern therapy for tuberculosis is to control themultiplicationoftheresistantmutants. Thiscanbeachievedbyusingmultipledrugregimens(n otlessthanthreeanti-tuberculardrugs)whichcancontroltheresistantmutant sto10-18 times. Wild type bacilli are more resistant and survive whileothers which show resistance to only single drug will be destroyed[5-8].

Multidrug Transportation:

Multidrugtransporterscontaintrans-membraneeffluxproteinsthatactivelypumpoutabroad rangeofcompoundsfromtheinteriorofthecell,usingeit herprotonmotiveforceorATPsuppliedenergy.Theyar eresponsible for acquiring resistance of a multitude of organisms tovariousdrugs.

P-glycoproteinisahumananalogueofthesemultidrugtra nsportersand is expressed on immune effector cells. Infection by M. tuberculosisresultsinincreasedexpressionofP-glycoproteinanddecreasedaccumulationof Isoniazid and Rifampicin inside the cells[9-11].

Occurrenceofresistancetoanti-tuberculosistreatment

Incompleteandinadequatetreatment

It mainly occurs with usage of monotherapy (with single drug). Thismayalsobeduetoignorance,useofpenicillin/strep tomycincombinations,useofrifampicinforotherdisea ses,andeconomicconstraints.

Inadequatetreatmentcompliance

Poorcomplianceduetoimproperknowledgeandcareis alsoresponsible for development of the resistance. Demographic factorsandsocio-economicstatusdonotshoweffectondegreeofcomplia ncewhilepsychologicalfactorscaneffectcompliance[12,13].

Relationbetweendoseanddrugresistance

A drug ForM.tuberculosis,duringtheinitialphaseoftreatment, theshapeoftheconcentration–timecurveisUshaped(Figure1)indicatingthatdrug exhibited its action. As the time passed, the curve changed toinverted U shape (Figure 2), indicating the development of resistanceofM.tuberculito drug[14].shows its action at different doses in different individuals.This is because a drug does not show same concentration versus timeprofile in allsubjects.

Itindicatesthatlowplasmadrugconcentrationscanlead toemergence of drug resistance. The response of the pathogen to aparticulardrugisrelatedtoconcentration–timeprofile.

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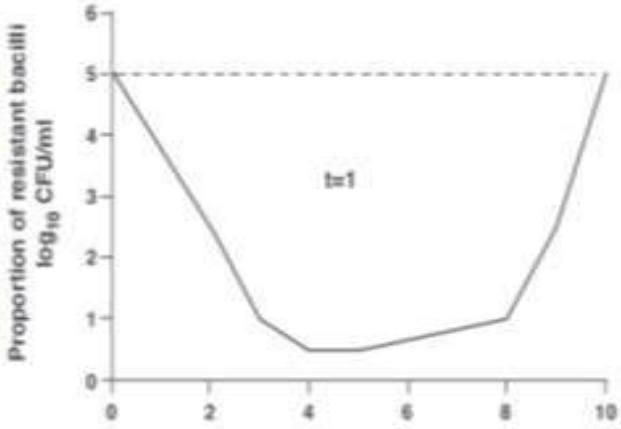

Figure1:concentration-timecurvefornon-resistance.

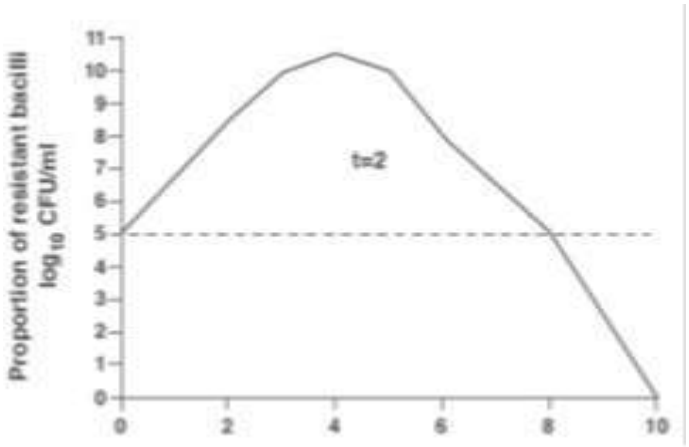

Figure2:concentration-timecurveforresistance.

Diagnosis

When multi drug resistant tuberculosis is suspected, it is confirmedby sending the patient's sputum to anti tubercular drug sensitivitytesting. The diagnosis of drug-resistant TB is made by performingDrug-Susceptibility Testing (DST) to the strain of TB obtained fromthepatient[15].

DiagnosticMethods

Patientswithdrug-resistantTBaredividedintothreemajorcategories.They are:

1. Thosewhoareincontactwithdrug-resistantTB.
2. Thosewhoarepreviouslytreated.
3. Thosewithinterruptedtherapy[16,17].

Conventionalmethods

Mostly,Lowenstein-Jensen(LJ)cultureisusedfordrugsensitivitytesting. Thedifferentconventionaldiagnosticmethodsare:

1. Absoluteconcentrationmethod
2. Theresistanceratiomethod
3. Theproportionsmethod

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Absoluteconcentrationmethod

In this method, the culture media and drug containing media isinoculated with a carefully controlled inoculum of M. tuberculosis.Minimum Inhibitory Concentration (MIC) of the drug is determined.Lower concentration of the drug inhibiting the growth indicates lesserresistance.

Theresistanceratiomethod

This method uses minimum inhibitory concentration of a standardsusceptiblestrainasstandardtoavoidvariations.

Theproportionsmethod

It is the method of choice for evaluating the drug resistance. Thismethod correlates the number of colonies increasing in size on drughold medium to the drug free medium. It designates the segment ofdrugresistantbacilliavailableinbacterialpopulation.

Modernmethods

Radiometricmethodsarebeingusednow-a-daysinordertodiagnosingtuberculosis.Oneofsuchmethodsis BACTEC-460(Becton- Dickinson) method. In this, a medium containing palmiticacid labeled with radioactive carbon is inoculated with mycobacteriawhich slowly metabolize the palmitic acid. Due to this, radioactivecarbon dioxide is released which is an indicator of bacterial growth[18-20]. The other most commonly used method is RFLP (RestrictionFragment Length Polymorphism) method. In this, fragment patternsareusedtocategorizetheisolatesoftheorganismsandcomparethemwitheachother[21].TheMycobacteriumGrowthIndicatorTube(MGIT) system is another method which is used for detection andsusceptibilitytesting.Thissystemutilizesanoxygen-sensitivefluorescent compound in a silicone plug placed at the bottom of tubecontaining the medium and is used to detect mycobacterial growth[22,23].

ObjectivesofAnti-TBTreatment

1. Rapiddeclineofbacterialcountwhichdecreasesmorbidityandmortalityandtoceasetransmission.
2. Preventtheoutbrokeofdrugresistantvariantstrains,and
3. Preventtheworseningofcondition.

PreventionofResistance

1. Isoniazid which is the most potent prophylactic drug is usedpredominantlyinthefirstweekfollowedbyrifampicintopreventresistance.
2. To avoid drug resistant variants, use multiple drugs which showsevidenceonefficacy.

Treatment is advised for adequately long period, with examiningofattachmenttotreatment,toeradicatetheremainingsurvivingorganismsthatareaccountableforthe worseningofcondition.

1. Almost all the successful mode of averting drug resistance is toadhere to the authoritative recommendations for treatment andmakesurethatalldosestakencorrectly.

Re-treatment

For patients classified as therapy failure the WHO recommends there-treatment regimen with in a span of eight months. The regimen ismade up of three drugs (isoniazid, rifampicin, and Ethambutol).

Inadditiontothis,pyrazinamideisspecifiedalloverthefirstthreemonths and streptomycin all over the first two months. Uncertaintymycobacterial culture and in vitro sensitivity testing are not regularlyconducted. Because, it is not feasible to institute whether these casesareevacuatingthemultidrug-resistantbacilli.Supplementalmanagementoforaloflo xacinwasestablishedtobepotentandsecureforthetreatmentofMDR-TB. Pefloxacinhavinghighsafety profileand is inexpensive so it was scrutinized to be an efficacious associatedrug inselected cases. Sparfloxacinisassimilated withkanamycinspecifiedduringthefirstthreetofourmonths.Andfinallyethionamidemanagementwashelpfulinattainingsputumconversion,clinical and radiological development. Other prophylactic agents likecarbapenemsexhibitoptimisticeffectandsupportableinincorporation with clavulanate for management of MDR-TB (Table 2)[24].

Resistancepattern	**Alternativetreatmentoptions**	**Duration of therapy(months)**
INH	RIF,PZA,EMB(FQ)	6-9
RIF	INH,PZA,EMB,STRorINH,PZA, EMB, FQ (STR)	9

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INH,RIF,PZA	FQ, INJ, second-line therapy	24
PZA	INH,RIF,EMB	9
EMB: Ethambutol; FQ: Fluoroquinolone; INH: isoniazid; INJ: Injectable Agent(Capreomycin, Kanamycin, Amikacin); PZA: Pyrazinamide; RIF: Rifampin; STR:Streptomycin.		

Table2:Possibledrugadministrationsforpatientswithtuberculosiswithdiversestandardsofdrugresistance.

Neweranti-tuberculosisdrugs

TB medication has been persistent for a period of ten years andfrequently composed of acquiring ten pills per day to a greater extentfor a least possible of six months. In case of MDR-TB, twenty pills perday for 18-24 months. At present accessible second-line drugs used totreatMDR-TBarefourtotentimesmoreacceptabletofailthanstandard remedy for drug non resistant tuberculosis. This prolongedregimen is not only more expensive than first-line antibiotics, but alsoappears with severe toxic side effects and psychological stresses. Insequence to oppose MDR and XDRTB and the generally expand ofantibiotic unaffected TB strains, the requirement of newer anti-TBdrugs is upcoming. In 2012 and 2013, two new anti-tubercular drugswereapproved. TheyareBedaquilineandDelamanid.Bedaquiline(diarylquinoline derivative) acts by inhibiting bacterial ATP synthetaseandpossesspotentactivityagainstdrugresistantanddrugsensitiveM.tuberculosis. Delamanid (nitro imidazole derivative) acts by inhibitingsynthesisofcellwallcomponents.Inthelastfewmonths,asequenceofcompoundsholdanitroimidazopyrannucleusthatownantitubercularactivityhavebeendiscoveredandareundertrials[25].

Drugs under Trials

TMC207

ItisanoveldiarylquinolineandisalsoknownasR207910.Itactsbyexhibitingitseffectinvitroasanantibacterialagentagainstoxidative-reproduction,drug-susceptible,MDRM.tuberculosis,antibiotic-sensitive M. tuberculosis. It particularly prevents the mycobacterialATP-synthase, consequently decreasing bacterial energy output in theformof ATP molecules [25,26].

PA-824

Itisanitro-imidazolesderivative(nitroimidazo-oxazine).PA-824isa prodrug which needs stimulation by bacterial de-hydrogenase andnitro-reductase to obstruct mycolic acid (important constituent in celllayerofmycolatataxonresponsibleforpathogenicity)synthesis.Moxifloxacin and pyrazinamide are indicated as antibacterial agentsexhibitingtheiractivityagainsttuberculosisinmice[27,28].

OPC-67683

Itisadihydroimidazo-oxazole.Itpossessespotentantibacterialactivityagainstantibioticsusceptibleand MDRM.tuberculosisbothin invitroandinvivoconditions.Itactsbyinhibitingmycolicacidoutputinthe cell wall [29].

Thoughthefindingoflatestanti-TBdrugswithlessresistanceareinprogress under trials, their invention and expansion is quiet complexandexpensive ($800million to $1billion)

RecommendationsfortherapyofpatientswithMDR-TB

When susceptibility experiment investigations are accessible andthere is an opposition to isoniazid and rifampicin but with or withoutresistance to streptomycin. In the beginning period, an association ofethionamide, fluoroquinolone, and other bacteriostatic drugs such asethambutol,pyrazinamideandaminoglycosidelikekanamycin,amikacin,orcapreomycinareadministeredforthreemonthsuptothetimeofsputumtransformation.

In continuation phase, ethionamide, fluoroquinolone, and otherbacteriostaticdrugsuchasethambutolcanbeusedfornotlessthan18monthsfollowingstaintransformation.

On condition that there is resistance to rifampicin and ethambutolbutwithorwithoutresistancetostreptomycinthroughoutthestartingperiod and an association of ethionamide, fluoroquinolone and otherbacteriostaticdrugssuchascycloserine,pyrazinamide,andaminoglycosides like kanamycin, amikacin, or capreomycin are usedforthreemonths.

TB-DOTs(DirectlyObservedTreatment,ShortCourse)

DOTS programs have been developed to control the unacceptablefailure rates and to combat the resistance of drug resistant mutantsagainstanti-tubercular drugs.

ThemainfiveelementsofDOTSstrategyare:

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1. Thetherapymayrequirebeingcategorizedrathert hanstandardized;

Laboratory facilities may be required to supply resources for on-siteculture and antibiotic susceptibility testing;

2. Authenticsuppliesareanextensiveareaofexpensi vesecond-linedrugs;
3. To regulate the manifestations needed some operational studies and
4. Economicandscientificsupportfrominternationa lorganizationsand Western governments must be required moreover procuredfromlocalgovernments [30-32].

Preventivemeasures

1. Isolationoftheeffectedpatienttoaseparateroom andchangingtheairinsideaboutsixtimesforeveryh our.
2. Roomshouldbeventilatedusingultravioletlamps orHEPA

filterstosupplementventilation;

3. Useofdisposablemasksforpersonsenteringthero omtoavoidspreading.

Immunotherapy inMDR-TB

As M. tuberculae is pathogen, immune system improvement canplay a major role in combating the organisms. This can be achieved inanumber ofways:

1. Vaccination: Vaccination for tuberculosis stimulates the host'simmune system and protects the individual by enhancing theeradication of mycobacterial population. BCG vaccine (BacillusCalmetteGuerin):Itisthemostcommonly usedTBvaccinethoughothervaccinesarealsoavail ablewhichareunderuseandtrials. It is highly affordable and safe when compared to othervaccines. The BCG vaccine is usually administered at birth and atan early age of 4-6 weeks to provide protection against all kindsof tuberculosis. However, babies with HIV/AIDS should not bevaccinated. BCG vaccine is not generally given to adults as theresultsarevariable.
2. Cytokinetherapy:Itincludesadministrationofinter feron-γ(IFN-γ,500μthriceweekly)andinterferon-α(IFN-α,3MUthriceweekly).Theseinterferonshelpinacti vatingthemacrophageswhichinhibitmultiplicatio nofmycobacterialpopulation.
3. Miscellaneous: The miscellaneous agents mainly used includeThalidomide and pentoxifylline Other agents include levamisole,transferfactor,TransformingGrowthF actor(TGF)inhibitors,andagentsinvolved inIFN-α generation[33].

Surgery

Surgeryaccountsforlowerdeathratewithlessthan3.5 %thoughrespiratorycomplicationsmaypersist.

The important factors responsible for death rate are severe chestirradiation, pulmonary abscission, extreme pulmonary damage, anyothermicrobialinfectionsandsputumpositivity.

Conditions for performingsurgery:

1. PresenceofMDR-TBirrespectiveofprolongedtreatment;and/or
2. Substantial standards of drug resistance that are related withtreatmentcollapseorauxiliaryresistance.

Internalcavitary,necroticillnessinalobeofthelungwas modifiedduringabscissionwithoutdevelopingrespira toryinsufficiencyandextremepulmonaryhypertensio n[34-37].

Nutritionalsupport

Nutritional support plays a key role in treating MDR-TB patients.Thefirstlineandsecondlineanti-tuberculardrugsarehighlyefficaciousandcancauseab dominalpain,headache,nausea,dizzinessanddiarrhea interruptingwithfoodabsorption.Thisultimatelyresul tsin decreased body weight and weakness. Dietary supplementation insuchpatientsmustincludemilkandcodliveroil(Tabl e3)[38-40].

Typesofnut rients	Examples
Highcalorief oods	Banana,wholewheatbread,coconutmilk,avocados,chiaseeds,walnuts,pinenuts,blueberries.
Highproteinf oods	Eggs- 6 g per 1 large egg, Milk-8 g per 1 cup, whey protein-24 g per scoop, chicken breast-24 g per oz, canned legumes-20 g per 1 cup,peanuts-6gper2oz,cashews-6gper2oz,almonds-6gper2oz,greenpeas-7gper1cup,Wheatgerm-6gper1oz,groundnuts-38gper1cup.

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Vitamins	VitaminCrichjuiceslikeOrangejuice,apowerfulantioxidantthatcanhelpthebodytofightagainsttuberculosisbacillus.Carrot,tomato,gooseberry,andpineapplejuices.VitaminArichfoodslikeOrange,mango,papaya,sweetpumpkin,carrots.
Minerals	Zincrichfoodslikepumpkinseeds,darkchocolate,sesameseeds,watermelonseeds,wheatgerm,chickpeas,squashseeds.SeleniumrichfoodslikeBrazilnuts,fortifiedeggs,flax,spinach,beefliver,sardines.Ironrichfoodslikeredmeat,seafood,beans,apricots,raisins.

Table3:Nutritional chartforTB.

II. CONCLUSION

Notonlyregardingtuberculosis,butalsoinrelationtoothermicrobialandinfectiousdiseases,resistancetowardsantibioticsresultsintreatmentfailures,progressionofdiseaseandinfections.

So, treatment should be directed towards using drugs which eithersuppress the resistance of organisms towards antibiotics or improve theefficacy of other anti-TB drugs. Resistance repression is explained asone medication intercept the resistance to another, but not one drugintercept the resistance to itself. By taking appropriate measures andstrictly following the therapy, the MDR-TB might be suppressed to agreaterarea.

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