Multi-Drug Resistanst Tuberculosis & its Management

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Introduction :

The discovery of antitubercular drugs was one of the major medical achievement of the 20th century and the introduction of short course chemotherapy, gives us an most effective antitubercular regimen for successful treatment of Tuberculosis. The short course chemotherapy is also called 100% regimen. But unfortunately a major emerging problem has been the increasing identification of strains of M. Tuberculosis resistant to two or more first line drugs. Multi-drsug resistant tuberculosis have been seen with increasing frequency. They are infecting the community to such an extend that primary drug resistant might become an epidemiological and clinical problem.

Definition :

Drug resistant should be define before multi-drug resistant for better clarification. For definition of drug resistance, criteria may be oriented to the laboratory or to the bed side. So drug resistant may be defined as- "When the bacilli instead of being killed, continue to grow (in vitro) in the presence of high concentration of drugs"1. But definition from clinical stand points". The patient who harber the bacilli, no longer responses favourably after administration of that drug is called drug resistan[2]t".

Tubercle bacilli are capable of developing resistance to more than one drug simultaneously. That is why the question of multidrug resistant tuberculosis arises.

Definition of Multi-drug resistant tuberculosis should be given in two ways. When non or one of the two strong drugs (INH & Rifampicin) is resistant then definition is - "When resistance occur three or more than three drugs called MDR Tuberculosis"[3]. But when INH, Rif. both are resistant then definition can be given as follows :- " When resistance occur to INH & Rif. with or without other drugs is called Multi-drugs resistant tuberculosis"[4,5,32].

Clinical Type of Drug Resistance :

1. Primary drugs resistance :

When the patient is primarily infected with resistant strain[2,5] from another patient developing secondary resistance . The patient of primary resistance did not have prior treatment with antitubercular drug. It is also called genotypic drug resistance.

2. Secondary drug resistance :

It is called acquired drug resistance or phenotypic drug resistance. The secondary drug resistance develops during chemotherapy or the patient receives chemotherapy previously[5,25]. It is due to physician error or poor compliance of patient.

Another term is initial drug resistance which includes true primary drug resistance and

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undisclosed acquired resistance. Determination of level of initial drug resistance gives the picture of type of tuberscele bacilli in community and influence the design of initial regimen in that community[6,17,22].

Incidence of drug resistance in IDCH7 :

In IDCH, department of pathology, Sputum from 380 cases was randomly selected, of them 131 patient have pure growth, 79 for atpical mycobacteria, 52 for Myco. Tuberculosis. The resistances pattern is tabuled as follows :

Resistant pattern of mycobactrian TB.

Drugs	% of resistance
INH	6.4%
Streptomycin	5.8%
Ethambutol	5.8%
Rifampicin	16.4%

Resistant Pattern of atypical Mycobacteria.

Drugs	% of resistance
INH	35.4%
Streptomycin	21.4%
Ethambutol	41.8%
Rifampicin	62.1%

Overall resistant pattern

Drugs :	% of resistance :
INH	27.4%
Streptomycin	15.2%
Ethambutol	27.4%
Rifampicin	43.5%

Multi-drug resistant 12.6%. Mostly due to atypical Mycobacteria8.

To conclude, the high rate of resistance in this study does not represent the resistance pattern of our community. Definitely we have dealt with the complicated patient likely to have high resistance.

Factors responsible for Multi-drugs resistant :

1. Repeated good chemotherapy but for too short period.
2. Use of bad chemotherapy-i. e. use of single drug even for a short period.
3. Use of unreliable chemotherapy for example - Streptomycin + INH -bears less risk, INH + PAS; TB1/ETH/SM (twice weekly) +INH. If they are given in the initial phase.
4. Co-prescription-Addition of Vits, Iron or other suppliment with antitubercular drugs. Because supplimentary drugs are cheap, the patient will take only these, avoiding antitubercular drugs.
5. Addition of single drug to previously developed resistant therapy.
6. Use of Rifampicin for other disease & INH included in the some cough Syrup.
7. Ability to purchase antitubercular drugs without prescription .
8. Increase incidence of HIV infection[8,20].
9. Increase incidence of atypical Mycobactarium[21].

Clinical Criteria of drug resistance[9]

1 . Persistant positive sputum :

When the sputum of a patient remains positive three month after good chemotherapy but in severe cases this duration may be extended upto 5-6 month.

2. *Fall & rise phenomenon :*

This phenomenon frequently observed with inadequately treated patient. After the start of treatment total number of bacilli decrease rapidly due to destruction of drug sensative organism, where as resistant bacilli remains unaffected. Subsequently the resistant bacilli multiply approaching the original number.

3. *Radiological deterioration :*

This is the less reliable criteria for drug resistance because it may be due to concomittent pneumonia, pulmonary infarction or development of bronchogenic carcinoma.

4. *Culture & Sensitivity*

This is the reliable resistant test but it takes weeks or months. Or it may not be available at all. Because it requires highly specialised laboratory & skill personnel10,24.

Investigation :

When drug resistance is suspected some investigations are necessary. It may be either documentary or oriented to the laboratory.

A) Documentary :

1. The physician should findout what treatment the patient has had and inquiry should be done about the drugs, the dose, the rythm, the duration, wheather the therapy was supervised or not, information from clinic record card should be taken if possible,. It will often help to see the problem more clearly.
2. If the reason for failure is not obvious from record, explanation should be given to the patient that he is sputum positive and to give him best treatment his co-operation is needed. If he agrees about stoping drugs duration should be noted interms of weeks or months[11].

If he claims of taking drugs regularly, a reliable member of his family should be asked because the patient do not necessarily tell the truth- "N0 one likes to admit personal responsiblility when things go wrong"

B) Laboratory :

"Sputum should be send for culture and sensativity for AFB. Consideration of HIV infection should be done and investigate accordingly.

Treatment of MDR -TB :

The planning of treatment programme in a country with high prevalance of multi-drug resistant tuberculosis is difficult. One of the main aim is to avoidence of increase in incidence.

Principle of designing treatment :

1 If possible the only drugs to which the bacilli are certainly sensative that is the drugs which are not given previously should be used. The problem of cross resistance should be kept in mind[26].

2. Doubtful drugs; that drugs which was previously used but on full consideration, the bacilli may be suceptable to them can be used, if they are powerful drugs i. e. INH, Rif. Strept[12].

3 Reseve drugs can be used when-

a) In case of resistant to most of first line drugs.

b) Failure of clinical response to conventional chemotherapy

c) Where expert guidence is available to deal with toxic effects. The drugs are :

Amaikacin
Kanamycin
Ethionamide
Cyloserin
PAS
Rifabutin & flaxacin[13]

Combination of four or more drugs should be started[27]. When sputum become negative, one or two weaker or more toxic drugs should be stopped. When resistance study become available the regimen can be modified appropriately. Treatment should be continued 6 months after conversion of sputum negative by culture.

4. Tuberculosis control program in Bangladesh has started treatment of resistance cases as catagory two with following drugs[16].

Initial phase-

RHEZ - for 3 months.

Supplimented by Inj streptomycin daily in initial two months.

Contineous phase - RHZ- for further 6 months. If the sputum does not become negative after the initial 3 months then the initial phase can be continued upto months with that 4 drugs.

5. Surgery can be done under full coverage of antitubercular drugs. The nature of surgery will depends upto the site and extend of lesion[28].
6. In some centre BCG vaccination & antitubercular chemotherapy has been tried.

Prevention of developing MDR-TB:

1. *Isolation of the cases :*

   This will decrease the spread of drug resistant organism to the community.

2. Achievement of good chemotherapy which will ensure
   a) 100% sputum convertion
   b) No relapse.
   c) No resistance even given for a short period.
   d) Every regimen should contain atleast three drugs in initial phase.
3. Relapse and chronic cases should be treated after careful thinking and selection of appropriate therapy.
4. It is to make sure that all the drugs prescribe should be taken regularly and also for the full time.
5. C0-prescription should be avoided.

Prospect of MDR - TB :

1. The treatment can be successful but needs very skillful supervision and encouragement of patient to tolarate unpleasant side effect.
2. Success rate is very low when resistant occurs INH, Rif. Streptomycin and quete high if two or more companion drugs can go with rif[14,2].
3. Poor result are documented in HIV infection with Multidrug resistance tuberculosis with such combination[15,19].

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