Multi Drug Resistant Tuberculosis - An Old Emeny but A New Enigma

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Introduction :

The medical profession believed, that it knew everything about tuberculosis and had almost contained it. But "there is always some little thing that is too big for us." Unfortunately that little thing is our old foe- M. tuberculosis, with a new face - MDR TB. In order to understand this catastrophic phenomenon we have to refresh our knowledge as well as devise new ways to combat it.

Definition

When a patient of tuberuculosis harbours bacilli resistant to one or more anti-tuberculosis drugs, it is called drug resistant tuberculosis (DR TB)[1]. But multidrug resistant tuberculosis (MDR TB) is defined as a case of tuberculosis caused by a strain of M. tuberculosis that is resistant to both isoniazid and rifampicin, the two main anti-tuberculosis drugs, with or without resistance to other drugs[2].

An isolate of M. tuberculosis is considered resistant to a drug if the number of colonies on the drug-containing medium is >1% of the number of colonies on the drug -free plate[3].

Types of Resistance

A drug-resistant isolate can be categorized as exhibiting primary or secondary resistance.

Primary resistance means, presence of drug resistant bacilli in a patient who never received anti-tuberculosis drugs (or received anti-tuberculosis drugs for < 1 month). It indicates fresh infection in a healthy person from a patient excreting drug resistant bacilli. These cases are sometimes referred to as "Transmitted resistance"[4].

Primary resistance may occur from a wild strain of M. tuberculosis present in nature which has never been in contact with any anti-tuberculosis drug. It is referred to as "Natural resistance"[5].

Secondary resistance means, emergence of drug resistant bacilli in a patient who has received anti-TB chemotherapy (for at least 1 month). It is a man made phenomenon due to faulty treatment and non-compliance. It is also called "Acquired resistance"[6].

'Initial resistance' is another term which includes patients with primary resistance as well as those patients with undisclosed ocquired resistance who either do not remember prior treatment, refuse to disclose previous anti-TB chemotherapy or were not properly asked about the treatment history[7].

Epidemiology

1.7 billion people, i.e. one-third of the world population is infected with M. tuberculosis of whom approximately 16 million are suffering from the disease. Every year 8 million new cases are detected and 2.9 million deaths are attributed to this ancient killer[8].

In Bangladesh, 6 million people are estimated to be suffering from tuberculosis. Approximately a quarter million (0.26 millio) new cases and 80 thousand deaths occur annually[5].

Although once tuberculosis was thought to be on the wane, since the 80's, there was dramatic upturn in the prevalence of the disease. If this trend continues, the projected number of TB cases in 2005 will become 11.9 million from 7.5 million in 1990, an increase of 57.6%. This projection is shown in Figure-1. Total TB deaths are estimated to increase about 40%[8,9].

Tuberculosis is a curable disease and even such a large number of patients can be treated, the alarming point is that many of them are not susceptible to the conventional anti-tuberculosis drugs. Unfortunately these patients are suffering from MDR-TB, a virtual death sentence.

The prevalene of MDR-TB in various countries is shown in the following table :

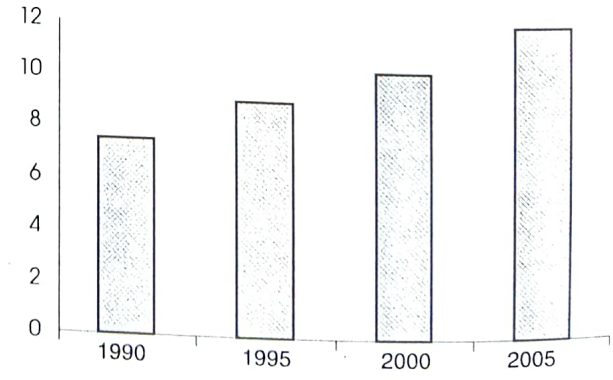

Fig-1

Table-1

Prevalence of multidrug resistant tuberculosis (MDR-TB)10

Study	Patients previously treated			Patients never treated		
	assessed (n)	acquired resistance (%)	MDR (%)	assessed (n)	primary resistance (%)	MDR (%)
Nepal	125	73.6	48	160	12.5	2.5
India	1574	80.2	33.8	570	19.6	0
New York City, USA	239	44	30.1	227	22.4	7.5
36 states (excluding NY city) USA	192	25.5	6.8	12980	11.9	3.2
Istambul, Turkey	260	53.4	21.5	525	26.7	3
Korea	138	49	18	276	17	0
Santa Cruz, Bolivia	372	43.4	15.3	636	16.9	0.9
Algiers, Algeria	581	20.8	12.7	1595	5.7	0.3
Tanzania	1550	18.7	4.2	1642	4.4	0.9
Western Cape, South Africa	1920	19.3	4	3928	6.3	1.1
Bangladesh	177	-	5.6	101	-	4.9

From this table, it is obvious that countries having an effective TB control program have a lower rate of MDR-TB.

Cases of MDR-TB are increasing day by day world wide. Figure -2 and Table-II shows that rapid rise of MDR-TB in New York City[11].

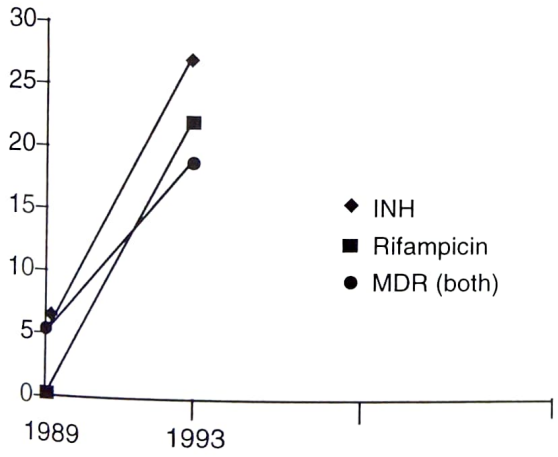

Table-II

Resistant to	1989	1993
INH	6%	26%
RIF	1%	22%
MDR	5%	19%

Problems of MDR-TB

1. Requires secondline drugs
2. Drugs are very toxic
3. Drugs are very expensive
4. Secondline drugs are not easily available
5. Duration of therapy is very long (minimum 15 months)
6. Hospitalization is mandatory :
   a) for intensive phase
   b) for prevention of transmission
7. Easily transmitted to health care workers.
8. High risk of nosocomial transmission.
9. Higher mortality in comparison to susceptible TB (median survival : 1.5 months vs 14.3 months).
10. Period of infectivity is longer. So a threat to effective control,.
11. Diagnosis of drug resistance is expensive, cumbersome and time-consuming.
12. Chances of treatment failure are 83 times more (11.6% vs 0.15%)*[7]
13. Chances of relapse is double[8].

Contributing Factors/Causes

MDR-TB is a man made phenomenon due to inffective administration of effective drugs, because in a properly treated patient it is virtually impossible for M. tuberculosis to become spontaneously resistant to both Rifampicin and INH.

The factors responsible for the resurgence of TB particularly MDR-TB are :

1. Epidemic of HIV infection and AIDS
2. Increase in high risk population e.g. homeless people, slum dwellers, drug addicts and malnourished patient.
3. Non compliance in taking prescribed anti-TB drugs.
4. Easy access to anti-TB medication i.e. over the counter, through quacks.
5. Erratic drugs ingestion
6. Poor bioavailability of drugs
   - malabsorption
   - questionable quality of drugs
7. Monotherapy :
   - from beginning
   - addition of single drug, on deterioration
8. Sub-optimal dosage and faulty combination.
9. Unmoniotred out-patient treatment of TB.
10. Weaknesses in implementation ofTB Control Strategy (irregular drug supply) .
11. Lack of uniformity in treament regimens between practitioners and TB control programmes.
12. Delay in laboratory diagnosis.
13. Expensive diagnostic procedures from MDR-TB.
14. Cavitary lesions[13].

Problems of HIV and TB

1. TB is commonest infection in HIV infected patients.
2. Mortality is 4 times higher in TB who are HIV positive.
3. HIV causes reactivitation of latent infection and may amplify the spread of TB.
4. Thiacetazone toxicity is increased.

Mechanism of Resistance

Since the exact modes of action of anti-TB drugs are partially understood, the mechanism of resistance is not totally clear. However, in view of the recent upsurg of MDR-TB, a considerable amount of work has been devoted to understanding mechanisms of resistance. The findings are summarized below :

Isoniazid : Antimycobacterial action of INH is mediated through the enzyme catalase peroxidase which is encoded by the katG gene[14]. Mutation in this gene leads to development of INH resistance.

Another gene inhA[15] encodes an enzyme which is involved in production of mycolic acid, a virulence factor of mycobacteria. Over expression of inhA gene leads to increased production of mycolic acid and ultimately causes resistance to INH.

Rifampicin : Mode of action of rifampicin is inteference with RNA transcription in the mycobacterial nucleus by binding to RNA polymarase which consists of a and ß subunits. The rpoB gene encodes ß-subunits. Mutations in this gene causes production of modified RNA polymerase. Refampicin fails to bind with this polymerase and hence cannot hamper RNA transcription, which results in emergence of rifampicin resistance[16].

Streptomycin : This drug acts on the S12 subunit of ribosomal protein of mycobacteria. S12 subunit is encoded by rpsL gene. Mutation in this gene results in production of altered S12 subunit, which is resistant to Steptomycin[17].

Pyrazinamide : Mechanism of action of pyrazinamide against mycobacteria is least understood than other anti-TB drugs. It is suggested that, pyrazinamidase, an enzyme, produced by M. tuberculosis converts pyrazinamide to pyrazinoic acid which inturn lowers the pH of the organism below the tolerable level. A mutation in this enzyme has been proposed as a possible mechanism of resistance[18].

Ethambutol : The mechanism of action has not been elucidated properly. However, mutation of gene encoding an enzyme called D- arabinase is thought to underlie the development of resistance.

Diagnosis

When to suspect MDR-TB ?

I) Retreatment failure : When a patient fails to respond to supervised standard WHO retreatment-

2 months	R	E	H	Z	S	Intensive
1 months	R	E	H	Z		
5 months	R	E	H			Continuation
Total 8 months						

Features of retreatment failure-

1. Persistently positive sputum smear

   a) Suspected retreatment failure : When patient shows persistently positive sputum smear even after 2-3 months of supervised chemotherapy, retreatment failure is suspected. However, if the bacilli count shows serial decline and the patient is showing clinical and radiological improvement the regimen should be continued.

   b) Genuine retreatment failure : When sputum smear is still positive after patient has completed 5-6 months of retreatment regimen regularly. The positive smear of some of these patients is attributable to presence of dead bacilli. They can be excluded by negative culture reports.

2. Culture positive

Positive culture is considered more authentic than smear positive.

3. Radiological deterioration

If radiological deterioration is not accompanied by biological deterioration, possibility of concurrent pulmonary disease should be borne in mind. Radiological deterioration alongwith bacteriological positivity is more indicative of retreatment failure.

4. Clinical deterioration

This is least reliable if not accompanied by bacteriological and radiological evidence of deterioration.

Clinical Features of MDR TB2 :

No marked difference from classical pulmonary TB. But,

- Cavitation occurs significantly more in MDR-TB. So, clinical features of cavitation are marked (copious sputum, hemoptysis).
- MDR-TB patients are more likely to have reticular interstitial shadows, which in case of classical TB is suggestive of healed tesion.
- Since MDR-TB is closely associated with AIDS, other systemic features of AIDS should be looked for.

II. Drug susceptibility results

At any stage of treatment or retreatment, if culture and drug susceptibility results show resistance to INH and rifampicin, MDR is established. However, a single report should be evaluated with caution.

Drug Susceptibility Testing

Indications :

1. Persons at high risk of infection with drug resistant organisms[19].
2. Patients with history of previous anti TB chemotherapy[19].
3. Contacts of known or suspected resistant cases[19].
4. Persons with life threatening forms of TB[19]
5. Patient needing retreatment regimen[19].
6. Patient showing increasing numbers of AFB after an initial decrease on sputum microscopy[20].
7. Patients with positive culture after 4-6 months of treatment[20].

Methods :

A. Using Lowenstein - Jensen medium[21] : requires > 4-6 weeks

   i) Absolute concentration method

   ii) Resistance ratio method

   iii) Proportion method

B. Using semi synthetic medium[23] (Middlebrook 7H10, 7H11) (by proportion method) : requires about 3 weeks.

C. Radiometric testing using BACTEC[24] : requires 1-3 weeks.

D. Polymerase chain reaction - single strand conformation Polymorphism (PCR-SSCP) methods[24]. requires 24 hours.

   It is comprised of intial amplification step (PCR) followed by demonstrating single strand conformation polymorphism (SSCP).

E. DNA finger printing[23].

F. Luciferase reporter phage[24]

Treatment

Chemotherapy

Drugs that can be utilized against MDR-TB are :

First-line anti-TB drugs

a) Streptomycin

b) Pyrazinamide- Acquired resistance against pyrazinamide is quite rare.

c) Ethambutol

d) Thioacetazone

The last two can only be used if reliable laboratory reports indicate susceptibility.

Second -line drugs

1) Aminoglycosides

a) Kanamycin - least expensive

b) Amikacin - more expensive

c) Capreomycin - most expensive

2. Thiomides

a) Ethionamide

b) Prothionamide - being used in Bangladesh

3. Cycloserine (or Terizidone)

4. Para aminosalicylic acid (PAS)

Newer Drugs

Fluoroquinolones -

Ciprofloxacin

Ofloxacin

Sparfloxacin (400 mg)

Levofloxacin

Rifamycins -

Rifabutin

Rifapentine

Clofazimine

Amoxycillin/Clavulanic acid

Macrolides

Clarithromycin

Azithromycin

Adjunct therapy

Interferon - gamma aerosol

Surgery

Immunization

(M. Vaccae)

Laser therapy

Fundamental Principles Involved in Planning of Drugs Regimen

1. A detailed drug history is of paramount importance.
2. Intensive phase should be under direct observation; preferably in hospitals (at least until sputum becomes negative).
3. Patient must be strongly motivated to ensure compliance
4. He/she should be completely aware about the gravieness of his disease and potentially serious side-effects of secondline drugs.
5. No need of keeping drugs in reserve.
6. The regimen should contain at least three drugs, preferably four or five, which have not been previously used by the patient.
7. A patient should receive a firstline drug to which susceptibility has been established by culture.
8. A combination of an injectable aminoglycoside and pyrazinamide has a satisfactory bactericidal activity.
9. Once sputum converts to negative, the weaker drugs should be gradually withdrawn with priority given to those with serious side effects.
10. Treatment should be continued for 18 months after sputum conversion.
11. Smear and culture should be performed on regular basis; monthly till sixth month and quarterly till the end of treatment.
12. Other concommitant illness or drug intake e.g. AIDS, Diabetes Mellitus, Corticosteroid intake should be ruled out.
13. Cross -resistance should be given due consideration

Thiacetazone and Ethionamide

Kanamycin and Amikacin

Cycloserine and Terizidone.

The ultimate choice depends on availability of susceptibility tests[25-29].

1) When susceptibility tests are not available -

Puase	Drugs	Duratin
Intensive	Aminoglycoside+Pyrazinamide+Ethionamide+Ofloxacin	3-4 months (till sputum conversion)
Continution	Ethionamide+Ofloxacin	18 months

II) When susceptibility tests are available

* Resistance to INH, Rifampicin and Streptomycin

Phase	Drugs	Duration
Intensive	Aminoglycoside, pyrazinamide, Ethionamide, Oflaxacin,	3 months
Continuation	Ethambutol, Ethionamide, Oflaxacin, Ethambutol	18 months

* Resistance to INH, Rifampicin and Streptomycin and Ethambutol

Phase	Drug	Duration
Intensive	Aminoglycoside, Pyrazinamide, Ethionamide, Oflaxacin,	3 months
continuotion	Cycloserine, Ethionamide, Oflaxacin, Cycloserine	18 months

Other regimens :

1)	Kanamycin, Pyrazinamide, Ethionamide, Cycloserine	3-4 months (or until sputum conversion)[10]
	Ethionamide, Cycloserine	15 months
2)	Kanamycin, Clofazimine, Oflaxocin, Pyrazinamide, INH, Ethambutol, Prothionamide, Oflaxocin, Pyrazinamide,	3 months[30]
	INH, Ethambutol, Prothionamide	12 months
	Ethambutol, Prothionamide	6 months
	[Ref. Hamid MA, Damien Foundation, personal communication]	
3)	Streptomycin, Ofloxacin, Pyrazinamide, Ethambutol	6 months[31]
	Ofloxacin, Pyrazinamide, Ethambutol	9 months

Surgery

Of 133 patients > 85% were converted to negative[32]

How to combat MDR-TB ?

Increased emphasis on DOTS

Limit nosocomial transmission

Conduct surveillance to determine patterns of drug susceptibility

Widen the capacity for rapid determination of drug susceptibility

Ensure easy availability of second line drugs.

HIV screening

Protectin of health care workers e.g. masks.

Recommendations for control of MDR-TB in Bangladesh

For Govt. of Bangladesh & National Tuberculosis Programme

1) Ensure country wide coverage by DOTS
2) Increase cure rate from 30% to desired level (70%)
3) Make anti-TB drugs available on prescription only
4) Establish central reference laboratory for culture and susceptibility testing.
5) Establish district chest clinic as referral centre for thanas within its jurisdiction
6) Entrust consultants at district chest clinic with supervisory role.
7) Increase budgetary allocation for chest clinics.

8 Increase number of beds in the divisional and segregation hospitals.

9) In districts without chest clinucs, 5% of medicine beds should be earmarked for chest and TB patients.

10) Make second line drugs easily available by

a) direct import through MBDC

b) allowing import of anti-TB drugs free of customs duty, VAT etc.

11) Ensure close coordination between NTP, NGOs and practitioners

For practitioners

1) The knowledge of all consultants, specialists and general practitioners about anti-TB drugs should be updated.

2) All these doctors should be convinced that simply prescribing drugs for patients is not enough. The ultimate success lies in ensuring compliance in TB patients by explaining the disastrous consequences of noncompliance like MDR-TB. For ensuring compliance, the physicians can nominate a family member as the "DOTS supervisor" for the patient. We should remember that our noncompliant patients shall ultimately become reservoirs of MDR-TB and subsequently may pass it on to us and our family members.

At social level

1) Social awareness about the resurgence of TB and its deadly multi-drug resistant form should be increased.

2) Elected representatives, government officials and local community leaders should be motivated for this purpose.

3) Remedies should be sought for problems like poverty and social injustice.

4) Formation of TB club for ensuring DOTS

References :

1. Crofton J, Chaulet P, Maher G. Guidelines for the management of drug-resistant tuberculosis. Global Tuiberculosis Program. WHO Geneva 1997:7.

2. Riley LW. Drug-resistant Tuiberculosis. Clin Inf Dis 1993; 17 (Suppl 2) : 5442-6.

3. Sommers HM, Good RC. Mycobacterium. In : Lennelte EH; Balows A. Husler WJ Jr. et al. (eds) Manual of Clinical Microbiology. 4th e. Washington DC, American Society of Microbiology, 1985; 216-48.

4. Jacobs RF. Multiple Drug-resistant Tuberculosis. Clin Inf Dis 1994; 9 : 1-10.

5. National Guidelines for tuberculosis Control. 2nd ed. TB and Leprosy Control Services, Dhaka 1995; p-22.

6. Treatment of tuberculosis. Guidelines for national programmes. WHO, Geneva 1993.

7. Khilnani GC, Sharma SK, Pande JN. Multi drug-resisntant TB. Indian J Chest Dis Allied Sci. 1994; 36(3) : 137-45.

8. Lutwick LI. Tuberculosis 1st ed. 1995. Champman & Mall London, p 2-53.

8. Lutwick LI. Tuberculosis 1st ed. 1995. Champman & Mall London p 20-53.

9. Centers for Disease Control and Prevention. Estimates of future global tuberculosis morbidity and mortality. MM WR.; 1993; 42 : 461-4.

10. t P, Raviglinone M, Bustreo F. Epidemiology, control and treatment of multi drug resistant tuberculosis. Drugs 1996; 52(2) : 103-7.

11. Frieden TR, Sterling T, Pablos - Mendez A et al. The emergence of drug-resistant tuberculosis in New York City N Engl J Med 1993; 133 : 423-430.

12. Mitchison DA, Nunn AJ, Influence of drug resistance on the response to short course chemotherapy of TB. Am Rev Respir Dis 1986; 133 : 423-430.

13. Reley LW, Arathoon E, Loverde VD. The epidemiologic patterns of drug resistant Mycobacterium Tuberculosis infections. Am Rev Respir Dis, 1989; 139 : 1282-5.

14. Zhang Y, Heym B, Allen B, Young D, Cote S. The catalase- peroxidase gene nd isoniazid resistance of mycobacterium Tuberculosis. Natue 1992; 358 : 591-593.

15. Heym B, Honore N, Truffont - Penst C et al. The implementing of multi drug resistance for the future of short course chemotherapy of Tuberculosis : a molecular study. lancet 1994; 344 : 293-298.

16. Jin DJ, Gross CA. Mapping and sequencingof mtations in the E. coli rpo B gene that lead to rifampicin resistance. J Mol Biol 1988; 22 : 45-58.

17. Meier A, Kirschner P, Bange FC, Vogel U, Bottger EC. Genetic alterations in stepthomycin-resistant Mycobacterium tuberculosis : mapping of multations conferring resistance. Antimicrob Agent Mycobacterium tuberculosis : mapping of mutations conferring resistance. Antimicrob Agents Chemother 1994; 38 : 228-33.

18. Cynamon MH, Klemens SP. Antimycobacterial activity of a series ofpyrazinoic acid esters. J Med Chem. 1992; 35 : 1212-5.

19. Bass JB, Farer LS, Hopewell Pc et al. Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis, 1990; 142 725-35.

20. Levi MH. The microbiology of tuberculosis. In : Lutwick LI, Ed. Tuberculosis - a clincial hand book. London, Chamman & Hall 1995; 154-82.

21. Vareldzis BP, Grosset J, de Kantor et al. Drug resistant tuberculosis. Laboratory issues, World Helath Organisation recommendatins. Tuberc Lung Dis 1994; 75 : 1-7.

22. Orita M, Suzulhi Y, Sekiya T, Hayashi K. Rapid and sensitivity detection of point tmutation and DNA polymorphism using the PCR. Genomics, 1989; 5 : 874-879.

23. Hermans PWM, Van Soolingen D, Dale JW et al. Insertion element IS686 form Mycobacterium tuberculosis : diagnosis and epidemiology of tuberculosis. J Clin Micro biol 1990; 28 2051-2058.

24. Jacobs WR Jr. Barietrta RG, udani R et al. Rapid assessment of drug susceptibities of mycobacterium tuberculosis my means of luciferase reporterphasges. Science 1993; 260 : 819-822.

25. AliKhaed N, Benadjiia H, Louci MS et al. Enquite therapeutique controlee sur trois reqgimen, Bull iInt Union Tuberc. 1976; 1 : 9-16.

26. Sai OB, Alouch JA, Githui WA et al. Controlled clinical trials of a regimens of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. Tubercl 1998; 69 : 5-4.

27. Goble M, Iseman MD, Madsen LA et al. Treatment of 171 patients with pulmonary tuberculosis resistant to isonizazid and rifampicin. N Engl J Med 1993; 328 : 537-42.

28. Iseman MD. Treatment of multi drug resistant tuberculosis.N Engl J Med 1993; 329 : 781-91.

29. Bouvet E. Les tuberculosis multiresistantes. Press Med 1995; 25 8 : 393-8.

30. Hamid MA. Damien Foundation, Bangladesh. Personal communication.

31. Managunnegro H, Tulac AD, Hudoyo A. The efficacy of low dose ofloxacin in the treatment of multi drug resistant tuberculosis in Indonesia. Int J Tuberc Lung Dis. 1998; 2(11) : suppl 2 : s178.

32. Powell LA, Iseman MD. The role of surgery in the treatment of drug resistant pulmonary tuberculosis. Int J Tuberc Lung Dis. 1998; 2(11) suppl 2 : s373.