Review Article

MULTIDRUG RESISTANT TUBERCULOSIS - BIOMECHANISM, EPIDEMIOLOGY AND MANAGEMENT STRATEGIES

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ABSTRACT

Multidrug resistant tuberculosis has shown an alarming increase and this assumes added importance in view of the increasing number of HIV infected patients. This article reviews the biomechanism of resistance and discusses the present strategies that are available and recommended to tackle the rising incidence of tuberculosis due to resistant mycobacteria.

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KEYWORDS: Antitubercular drugs; Drug resistance; *Mycobacterium tuberculosis*.

Introduction

Tuberculosis (TB) is still the single largest cause of disease and death by a single infectious agent. In spite of availability of very effective treatment for over last 3 decades it continues to cause about 7 per cent of global mortality and it is rising. The WHO estimates that worldwide about 10 crore people may be infected with drug resistant tubercle bacilli. Three crore of these would be having multidrug resistant tuberculosis (MDRTB). The whole scenario is further complicated by spread of MDRTB to new cases and to HIV infected cases.

Resistance of mycobacteria was defined by Mitchison in 1961 as a temporary or permanent capacity of organisms and their progeny to remain viable or to multiply in presence of concentration of drug that would normally destroy or inhibit the growth of other similar cells.

However, resistance to various antitubercular drugs in natural wild strains was known as early as the late seventies [1]. Era of modern and effective chemotherapy really began in 1952 and as world wide TB control programmes began addition of newer drugs brightened hopes. But human shortcomings created situations of ineffective therapy.

This led to the beginning of development of drug resistance by mycobacterium to various drugs [2,3]. In 1965 Canetti [4] warned that global feeling is that resistance to drug in mycobacteria has slipped into history but today the medical community has learnt the hard way [5-7].

Definitions

Initial resistance - denotes drug resistance in patients who deny a history of any previous chemotherapy.

Acquired resistance - Patients who initially have a drug sensitive infection but later become resistant due to inadequate or inappropriate therapy.

Multidrug resistance (MDR) - Ideally any patient showing resistance to two or more antitubercular drugs is to be considered as MDR, however the prevailing view, like that of Iseman [6], is to consider only INH and rifampicin resistance as MDR. This is due to the fact that these cases have a much worse outcome [7,8].

Molecular mechanisms of resistance

Tubercle bacilli have a spontaneous predictable rate of chromosomal mutations that confer

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Fig. 1 :

resistance to antimicrobial agents. These mutations are unlinked. For isoniazid (INH) and Rifampicin (Rif) there is about 1 mutation in 10^8 to 10^9 replications [9]. Thus mutants resistant to both INH and Rif will be a result of above 2 possibilities, i.e. 1 in 10^{16} , and so development of spontaneous dual resistance is highly improbable. However when there is inadequate chemotherapy due to any cause (Fig 1) sensitive bacilli are killed and resistant ones keep on growing to ultimately become the dominant form of the bacterial load for that patient and if at that stage drugs are added serially and inadequately mutants resistant to the new drugs are again selected and patient will land up with bacteria resistant to 2-3 or more of the chemotherapeutic agents. This scenario is referred to as serial selection of drug resistance and is the predominant mechanism of MDR [5,10].

More recently, a new phenomenon has emerged, i.e. transmission of MDR strains to new contacts and then outbreaks MDRTB. Here the bacteria is primarily resistant to multiple drugs from the beginning itself. Though in many areas this has occurred more frequently with contact of HIV positive cases [11,12], MDRTB outbreaks have also occurred in HIV negative people [13,14].

Survey of initial MDRTB cases in a community has become very important for redesigning the regimen for new cases and planning appropriate regimen for cases requiring retreatment. In many countries, repeated regular surveys have shown the value of such surveys [15].

Molecular mechanisms of drug resistance in *M. tuberculosis* remained largely unknown until recently. Plasmids or transposons have not been found to cause drug resistance in *M. tuberculosis*; rather chromosomal mutations are responsible. Recent molecular analysis of some MDRTB strains suggests that the MDR phenotype is caused by sequential accumulation of individual mutations in separate genes, not by novel mechanisms due to single mutagenic events [16]. Broadly speaking, based on the specificity of anti-TB drugs, drug resistance mechanisms in *M. tuberculosis* can be divided into specific and non-specific mechanism. The tuberculosis-specific drugs (isoniazid, pyrazinamide, ethambutol and others) attack unique metabolic pathways in *M. tuberculosis* and are relatively ineffective against other bacteria. Mechanisms of resistance to these drugs are unique to *M. tuberculosis* and so far only isoniazid (INH) resistance mechanism have been characterised [17,18]. However, the mechanisms of resistance to drugs

not tuberculosis-specific drugs (streptomycin, rifampicin, fluoroquinolones) are well advanced. The mechanisms of resistance in *M. tuberculosis* are analogous to those found in other bacteria. The identification of mutations responsible for drug resistance in *M. tuberculosis* offers a new means for rapid detection of drug resistant isolates by PCR based techniques.

Implications in an individual patient

The implications for MDRTB for individuals are quite profound and are: (a) a 83-fold risk of treatment failure and 2-fold risk of relapse [19], (b) a vastly extended duration of chemotherapy, (c) a much higher risk of drug toxicity, (d) a potential need for surgical intervention, and (e) increased expenses for treatment.

In the developing world with few resources and poor infrastructure MDRTB cases are considered to be untreatable [20] and constitute a dangerous reservoir of MDR bacilli and a source of MDR infection with initial or primary resistance to many new contacts in the community.

In a study published in JAMA a crude assessment of resistance to any drug was 14.2 per cent. It was 21.6 per cent in children below 15 yr and 9.4 per cent in patients aged 64 yr and above thereby suggesting a dangerous trend that over the years progress of resistance has been dangerously increasing.

Similar figures for some other countries are also available [21,22]. An assessment of actual state of drug resistance from a vast country like ours with highly inadequate data collection and reporting may be fallacious but the extent of the problem seems to be very great. Survey of many patients from various cities of different states of India show an alarming rate of INH and streptomycin (SM) resistance (33 to 74%), and also a sharp increase in rifampicin resistance (23%) [23,24]. Resistance rates for INH and SM from some places in India are shown in Table 1, though these are obviously from small selected groups. Another recent assessment from Delhi confirms the rising incidence of MDRTB, being found in 23 to 28 percent of cases [25]. An assessment of data of the past few years at our institute also confirms that above fears are not without basis (Table 2).

TABLE 1

Resistance against INH and Streptomycin

	INH%	SM%	One or both drug%
Agra	48	45	58
Amritsar	26	24	33
Bombay	29	35	39
Calcutta	69	63	74
Delhi	26	18	33

TABLE 2

MH (CTC) Pune data on drug resistant tuberculosis 1992 to 1994

	1992	1993	1994
Single drug Resistance	14	41	38
Two drug Resistance	18	26	28
Three or more drug Resistance	5	15	13
Total	37	82	79

Management of MDRTB

A high index of suspicion for resistance to standard drug regimen is more important in this disease than in any other situations because of the grave risk of community spread of MDRTB if diagnosis is delayed [26]. Chances of cure are reduced unless effective regimen is instituted early [27].

Important Diagnostic Steps

History: Any history of contact with a known case of drug resistant TB case should arouse suspicion. Antitubercular drugs taken previously should be recorded carefully as an accurate history is of great help in diagnosis. One should record carefully (a) drugs used irregularly or monotherapy taken in past, (b) drugs used regularly in adequate dose but for shorter than desired period, (c) drugs never used, (d) incidence of cross resistance among drugs.

Clinical evaluation: Drug resistance should be suspected in the following situations: (a) if after 10-12 weeks of adequate combination of drugs given under supervision patient fails to show a clinical response, (b) if serial chest radiographs show a deterioration in the existing lesions, or appearance of fresh lesions, or increasing or fresh

TABLE 3
Suggested regimens for the treatment of MDR TB

Resistance to	Suggested treatment	Duration	Surgery
Isoniazid Streptomycin	Rifampicin Pyrazinamide Ethambutol Amikacin	6-9 months	Should not be needed
Isoniazid and Ethambutol +/- Streptomycin	Rifampicin Pyrazinamide Ciprofloxacin Amikacin	6-12 months	Should not be needed
Isoniazid and Rifampicin +/- Streptomycin	Rifampicin Ethambutol Ciprofloxacin Amikacin	18-24 months	Consider
Isoniazid and Rifampicin Ethambutol +/- Streptomycin	Rifampicin Ciprofloxacin Amikacin Plus 2 Others*	24 months after conversion	Consider
Isoniazid and Rifampicin +/- Streptomycin	Ethambutol Ciprofloxacin Amikacin Plus 2 Others*	24 months after conversion	Consider
Isoniazid and Rifampicin and Pyrazinamide and Ethambutol +/- Streptomycin	Ciprofloxacin Amikacin Plus 3 Others*	24 months after conversion	If possible

Choose from ethionamide, cycloserine, paraaminosalicylic acid. Adapted from Iseman MD. Treatment of multidrug resistant tuberculosis. NEJM. 1993; 329 : 784-91.

cavitation, (c) if fall-and-rise phenomenon occurs in examination of sputum for AFB, (d) if despite adequate and supervised antitubercular therapy, sputum remains positive for AFB for over 12 to 16 weeks.

Laboratory diagnosis: The confirmation of presence of drug resistant bacteria can be done from culture and sensitivity test. This can be done by help of either 7H10 or 7H11 Middlebrook or LJ media. If patient is AFB positive then direct incorporation of the drug in the medium will facilitate results to be available in 6 to 8 weeks. But in sputum negative and culture positive groups, drug sensitivity tests will have to be carried out after bacilli are cultured and the total duration taken is 12 to 16 weeks. Newer rapid methods like a rapid

slide culture, the BACTEC system (which measures tagged CO₂ output), and the Luciferase Reporter mycobacteriophage test (using a bacteriophage with a cloned gene) are being tried.

Principles of Chemotherapy

Treatment of drug resistance in pulmonary TB is a challenge. Problem is compounded because one has to depend on (a) less potent drugs, (b) potentially more toxic drugs, (c) 4 to 5 or more toxic drugs, (c) prohibitively costly medicines, (d) much prolonged duration of therapy and, (e) significantly increased relapses.

Drugs against MDRTB are basically divided into following groups:

(a) First line drugs: Drugs not used earlier or not

used for a sufficient length of time. This include INH, Rif, pyrazinamide (PZA), SM and ethambutol (Emb).

(b) Second line drugs: Kanamycin, capreomycin, viomycin, amikacin, cycloserine, ethionamide, prothionamide, paraaminosalicylic acid (PAS), thiacetazone.

(c) Newer drugs

- i. Quinolones: Ciprofloxacin, ofloxacin, sparfloxacin, lomefloxacin, clinafloxacin, OPC 17116.
- ii. Rifampicin derivatives: Rifabutin, rifapentine, KRM1648 (KANEKA), SPA-S-165, SPA + Glaxo.
- iii. Macrolides: Roxithromycin, clarithromycin, azithromycin.
- iv. Beta lactam antibiotics with clavulanic acid.
- v. Cephalosporins: Cefornide.
- vi. Folate Antagonists*: Trimethoprim derivatives, metioprime, K130 (Dihydrofolate reductase inhibitor).
- vii. Oxazolidinones: U 97456.
- viii. Miscellaneous*: Azaquinone (Gangamycin)-Fusidic Acid.
- ix. Immunomodulators*: Interferon γ , Interleukin 2, TNF, *Mycobacterium vaccae* immunotherapy.

Those marked * are as yet experimental. Regimes suggested for MDRTB are shown in Table 3.

Monitoring of retreatment

Clinical response:- Repeated clinical evaluation of patients is very important as it gives an idea of efficacy before radiological and bacteriological profile is known. One must record temperature, body weight, presence of cough and malaise.

Sputum examination:- Bacterial counts are to be done every week to assess bacterial burden. Once negative examination should be done monthly. Sputum culture and AST should be done every 3 months till the end of therapy.

Chest radiography:- This should be repeated at 6 to 8 week intervals.

Role of laser in management

Trials with lasers were first done in Russia and

later in Indore in India. Laser therapy is supposed to act by decreasing bacterial load in moderately advanced disease. It improves penetration of drugs in walled-off lesions and helps in cavity closure. It is also valuable in management of tracheal or bronchial stenosis due to granuloma. The types of lasers used include N₂, CO₂, YAG, He, and Neon laser [28, 29].

Role of resectional surgery

Due to frequent treatment failure in spite of all the drug combinations, planned surgical intervention is now increasingly used as an adjunct to medical therapy. The main aim is to drastically reduce the bacterial load. In cases of localized disease with good cardiopulmonary reserve, resection of cavities or lobes may be done. In such a series of 57 patients reported by Mahmuddi & Iseman [30], 49 had good clinical and bacteriological response. Complications like bronchial disruptions with fistula, and respiratory insufficiency were seen in a few.

Immunotherapy with *Mycobacterium vaccae*

There has been a rekindling of interest in immunomodulation and immunoenhancement. Some breakthrough seems to have been achieved by using the heat killed suspension of *M. vaccae*, the preferred strain being NCTC 11659 [31,32]. A dose of 10^9 bacteria, equivalent to wet weight of 1 mg, is injected into the deltoid muscle [33]. It is reported to be free of any side effects and the mode of action is still elusive. Antibody production is promoted by production of enhancement maturation of T helper cells type-2 (TH2). Studies have been done in Iran [34], Romania, Vietnam and a study is in progress at Calicut in India using this mycobacterium. In the Iranian studies, out of 100 patients of MDRTB, only one had achieved bacteriologic cure after chemotherapy. By addition of up to 4 injections of *M. vaccae*, 11 of 42 patients were successfully cured and remained sputum negative for AFB for at least next 2 years follow-up. It was then inferred that *M. vaccae* immunisation along with chemotherapy for MDRTB showed considerable improvement in the results.

Prevention of MDRTB

There are 3 main approaches to the prevention of MDRTB.

(a) Identification and treatment of MDR tuberculosis patients with the aim to cure them and prevent further transmission.

(b) Chemoprophylaxis of susceptible contacts of MDR cases like children and HIV positive cases.

(c) Effective monitoring of all tuberculosis cases to development of any acquired resistance due to incomplete therapy.

Conclusion

At no time in recent history has TB caused such concern as it has today. So if the governments of the affluent and the developing countries like India think of tuberculosis resurgence as a burden of the poor and underprivileged, and do not wake up now to straighten out their priorities of spending for medicare, then sure we are all sitting on the edge of a crater of doom as described by Murray in IUALTD bulletin of 1990 [35].

Key to success remains the provision of support for adequate case finding and treatment of cases. There should be more application of directly observed therapy, integrating other services including the HIV screening and control measures [36]. Difficulties of motivating the administrators at all levels including those in the government are well described by Chakravorty [37] and Jain [38]. Drug resistance and role of HIV disease in tuberculosis resurgence are already straining the meagre resources of health care of developing countries to the limit. If we have to carve out a future, then all out efforts at all levels at whatever the cost is the need of the hour.

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