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Review Article

Multi-drug resistant tuberculosis burden and risk factors: An update

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Abstract

Multi-drug resistant (MDR) tuberculosis is defined as disease caused by *Mycobacterium tuberculosis* with resistance to at least two anti-tubercular drugs Isoniazid and Rifampicin. Recent surveillance data have revealed that prevalence of the drug resistant tuberculosis has risen to the highest rate ever recorded in the history. Drug resistant tuberculosis generally arises through the selection of mutated strains by inadequate therapy. The most powerful predictor of the presence of MDR-TB is a history of treatment of TB. Shortage of drugs has been one of the most common reasons for the inadequacy of the initial anti-TB regimen, especially in resource poor settings. Other major issues significantly contributing to the higher complexity of the treatment of MDR-TB is the increased cost of treatment. Other factors also play important role in the development of MDR-TB such as poor administrative control on purchase and distribution of the drugs with no proper mechanism on quality control and bioavailability tests. Tuberculosis control program implemented in past has also partially contributed to the development of drug resistance due to poor follow up and infrastructure. The association known for centuries between TB and poverty also applies to MDR-TB, a rather significant inverse association with MDR-TB. Various treatment strategies have been employed, including the use of standardised treatment regimens based upon representative local susceptibility patterns, empirical treatment based upon previous treatment history and local Drug Susceptibility Test (DST) patterns, and individualised treatment designed on the basis of individual DST results. Treatment outcomes among MDR-TB cases have varied widely; a recent survey of five Green Line Committee (GLC) approved sites in resource-limited countries found treatment success rates of 70%. Treatment continues to be limited in the resource poor countries where the demand is high. The ultimate strategy to control multidrug resistant tuberculosis is one that implements comprehensive approach incorporating treatment of multidrug-resistant tuberculosis based upon principles closely related to those of its general DOTS strategy for TB control: sustained political commitment; a rational case-finding strategy including accurate, timely diagnosis through quality assured culture and DST; appropriate treatment strategies that use second-line drugs under proper case management conditions; uninterrupted supply of quality-assured antituberculosis drugs; standardised recording and reporting system.

Key words: DOTS Plus, Multi drug resistant (MDR) tuberculosis burden, risk factors.

Tuberculosis is a medical, social and economic disaster of immense magnitude and has received substantial attention in recent years from general public and scientific communities[1]. The World Health Organisation estimates that 32% of the world population is infected with *Mycobacterium tuberculosis*, the causative agent of TB[2]. There were an estimated 9.2 million new TB cases and 1.7 million deaths from TB in 2006[3]. Control of tuberculosis (TB) remains one of the most serious challenges to global health. Another new and potentially devastating threat to TB control is the emergence of strains that cannot be cured by standard anti-tuberculosis drug regimen. Drug resistant tuberculosis generally arises through the selection of mutated strains by inadequate chemotherapy. Resistant to at least two major antitubercular drugs Isoniazid and Rifampicin has been termed as multidrug resistant tuberculosis[4]. On the basis of the drug sensitivity tests carried out on more than 90,000 patients in 81 countries, the WHO and IULTD reported more cases of resistant TB over the period of 2002 till 2007 than ever before. This large set of data has yielded improved estimates of the scale of resistance problem worldwide, indicating 289,000 MDR-TB cases among new patients (3.1%) and 221,000 MDR-TB among previously treated patients (19%) in 2007[5].

Since the introduction of the first effective anti-TB drug, streptomycin (SM), in the late 1940's, resistance

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of *Mycobacterium tuberculosis* to chemotherapeutic agents has been understood as a major problem in the management of TB disease. Clinical relapse after three to six months of improvement was observed in the earliest studies of streptomycin[6]. Randomised controlled trials carried out by British researchers upon the introduction of PAS in 1948 found that patients receiving combined therapy (PAS and SM) had lower rates of relapse than those receiving either drug alone[7]. As the tuberculosis chemotherapy era evolved, increasing cases of drug resistance continued to occur mainly as a result of inadequate regimens and non-adherence to therapy[8]. The fight against TB in the last two decades has been further challenged with the emergence of two key obstacles: The first man-made phenomenon is the emergence of the resistant forms of TB, against which the treatment is much more difficult and at times impossible. The second obstacles have been the emergence and pandemic spread of the Human Immunodeficiency Virus (HIV).

Tuberculosis drug resistance can be either primary (transmission of resistant organisms) or secondary (resistance acquired in the host related to inadequate treatment). There are four broad categories of mechanisms of acquired resistance to drugs by *M. tuberculosis:* 1) the creation of a lipid-rich cell wall that can reduce the permeability of drugs (and arrest phagasome maturation); 2) the production of enzymes that degrade or modify compounds, rendering them useless; 3) the efflux of drugs through protein pumps, described for Isoniazid and Ethambutol; and 4) spontaneous chromosomal mutations that affect key drug targets[9]. Among these, the fourth mechanism is considered to be the most important. Mobile or horizontal transmission of resistance, such as plasmid mediated resistance, does not occur in *M. tuberculosis.* Random genetic mutations occur with low but predictable frequencies in the range of one mutation per 10^6 to 10^9 organisms. The frequency of mutations conferring resistance to particular agents varies from the range of 10^3 for many second line drugs (Thiacetazone, Ethionamide, Capreomycin, Cycloserine, and Viomycin) to an intermediate level (around 10^6) for some first and second line drugs (Isoniazid, Streptomycin, Ethambutol, Kanamycin, and Pamino salicylic acid) to the lowest levels for Rifampicin, on the order of 10^8 to 10^{10}. When large populations of *M. tuberculosis* are formed in a host and selective pressure is placed by a chemotherapeutic agent, the small population of *M. tuberculosis* that has evolved resistance to the agent will continue to multiply while the susceptible *M. tuberculosis* is suppressed. This enables the drug resistant organism to become the dominant organism in the host[10]. In order to prevent this scenario from occurring, the central strategies in therapy are to: 1) administer several chemotherapeutic agents, such that if there are organisms resistant to one or two agents, they will be killed by the other agents; 2) provide therapy for an adequate duration in order to ensure eradication of populations of *M. tuberculosis*, which evades both host immune response and drug actions by a number of intricate cellular mechanisms[10]. Because the probability of two simultaneous mutations- the product of the individual probabilities of mutations—is small (10-11 to 10-14) compared with typical bacillary loads (up to 109 in a pulmonary cavity), the sustained presence of two or more effective drugs should eradicate the entire population of bacilli (this traditional model, while useful, is an oversimplification due to the formation of microenvironments with differing drug concentrations and activities[10]. Not surprisingly, the most common ways in which *M. tuberculosis* drug resistance evolves or amplifies in the host involve the violation of these principles. The causes of these violations range widely, from the actions of the individuals, by non adherence, to those of the health provider, by improper regimen selection or suboptimal dosing, to the failure of TB control programs to provide a consistent supply of necessary agents[9]. Understanding of these causes has evolved considerably over the past two decades, trending towards increasing recognition of the impact of the social, economic and political environments in which therapy takes place upon the likelihood that patients will be exposed to the proper treatment for an adequate duration[11, 12].

Numerous host factors have been implicated in the facilitation of acquired drug resistance, including the development of local tissue microenvironments recalcitrant to antibiotic penetration or activity and the failure of the immune system to act in synergy with antibiotic activity[10]. Compromise of the host immune response caused by infection with HIV may be a significant risk factor for the evolution of drug resistance.

Emergence of multidrug resistant tuberculosis

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least Isoniazid and Rifampicin (the two most important first-line drugs), appeared after the introduction of Rifampicin in 1966. Unit 1990, however, most MDR cases occurred in patients receiving prolonged, inappropriate therapy; while sporadic outbreaks of primary transmission occurred, the magnitude and impact was relatively limited[13]. In the early 1990's, several large outbreaks of MDR-TB unfolded in hospitals and institutions in the United States, announcing MDR-TB as a major public health threat[14, 15]. In New York City, where the largest number of MDR-TB cases was reported, as many as one in five TB cases involved MDR. Strong evidence of recent,

primary transmission of resistant TB was established. Among patients who had never been treated before, 23% were resistant to one or more drug[15]. Molecular fingerprinting by restriction fragment length polymorphism (RFLP) implicated a single strain in 22% of MDR cases in New York City in 1992[16]. High rates of nosocomial transmission, to health care workers and HIV positive patients in particular, were documented[14]. Together, these circumstances demonstrated the rapidity with which MDR-TB could spread through susceptible populations. the MDR-TB epidemics in New York and elsewhere in the country were brought under control and the incidence of MDR-TB plummeted[17] through a massive investment of human and financial resources (estimated by some to be as high as a billion dollars),. Subsequent nosocomial and institutional outbreaks in Italy, Spain, Russia and Chile made it clear that MDR-TB ranked among the most serious public health issues facing the world[18].

More recently, the use of chemotherapeutic agents with efficacy against tuberculosis for treatment and prophylaxis of other diseases has been implicated in the development of resistance to these drugs by *M. tuberculosis*. This includes empiric use of Quinolones for community acquired pneumonia, when in fact the patient is manifesting tuberculosis, or Aminoglycosides for a number of diseases[19, 20, 21]. Both are important second line tuberculosis classes that are widely used in routine clinical practice for the treatment of other diseases. The duration of exposure required for resistance to evolve has not been well characterized yet; nevertheless, this has led some high TB-prevalence countries to regulate empiric use of these classes of drugs. The use of Rifamycins in the prophylaxis of mycobacterium avium-intracellular disease has been associated with the development of Rifampicin-resistant TB in HIV patients[22, 23]. Finally, there exists considerable cross-resistance and class-resistance to antituberculosis agents. All Rifamycins have high levels of cross resistance. Fluoroquinolones have considerable cross resistance, but in vitro data suggests that newly introduced Fluoroquinolones may be effective when resistance to previous generation Fluoroquinolones is present (cross resistance within earlier quinolones, such as ciprofloxacin and Ofloxacin, is very high). Kanamycin and Amikacin have almost 100% cross resistance[24]. Streptomycin is believed to have low levels of cross resistance with Kanamycin and Amikacin[25].

MDR TB burden

Global data on the prevalence of MDR-TB, however, were lacking. The first global survey of TB drug resistance was published in 1997 by the Global Project on Anti-TB Drug Resistance, collaboration between the World Health Organization and the International Union against Tuberculosis and Lung Disease. Two subsequent global surveys, covering the periods of 1996 to 1999 and 1999 to 2002, further elucidated the worldwide picture of drug resistance[26]. The data published by the Global Project revealed that virtually all countries surveyed reported TB drug resistance and estimated that 424,000 cases of MDR-TB emerged in 2004. With the exception of Botswana, which was found to have rising rates of MDR-TB, no trend data was available from Africa, a result of the poor laboratory infrastructure and surveillance on the continent. Twenty sites worldwide reported drug resistant TB prevalence in excess of 20%, and eleven sites reported rates of MDR-TB among new cases of over 6.5%. The geographic distribution of MDR-TB is highly uneven and ranges from 0.7% in new cases in established market economies, to around 2% in Africa, Southeast Asia and South America, and over 10% in some areas of the former Soviet Union and several provinces in China. Among previously treated cases, the rate of MDR is often several fold higher; by 2002, nine settings had been identified as having MDR rates of above 30% in previously treated case[27].

As per anti-tuberculosis drug resistance in the world: fourth global report, the population weighted mean of MDR-TB among all TB cases from the 114 countries and 2 SARs of China is 5.3% (95% CLs, 3.9-6.6), but ranges from 0% in some western European countries to over 35% in some countries of the former Soviet Union. In terms of proportion, the countries of the former Soviet Union are facing a serious and widespread epidemic where the population weighted average of countries reporting indicates that almost half of all TB cases are resistant to at least one drug and every fifth case of TB will have MDR-TB. MDR-TB cases in this region have more extensive resistance patterns including some of the highest proportions of XDR-TB[28].

Following countries of the former Soviet Union, provinces in China reported the highest proportions of resistance, while Western Europe, followed by countries in Africa, reported the lowest proportions of MDR-TB. It is important to note at least one country in all six WHO regions has reported >3.0% MDR-TB among new cases. It was found that 489,139 (95% CLs, 455,093-614,215) MDR-TB cases emerged in 2006, and the global proportion of resistance among all TB cases is 4.6% (95% CLs, 4.6-6.0). China and India are estimated to carry 50% of the global burden of cases, and the Russian Federation is estimated to carry a further 7%. Data from surveys in ten of 31 provinces in China over a ten year period indicate that drug resistance is widespread and in terms of proportion ranked second to countries of the former Soviet Union, but China has the highest burden of cases in the world. It is estimated that

130,548 (97,633-164-900) MDR-TB cases emerged in 2006 or over 25% of the global burden[28].

Thus global survey revealed that, regional and national variation in the magnitude and trends in drug-resistant tuberculosis exits. Countries of the former Soviet Union, followed by some provinces of China, reported the highest prevalence of resistance, while Mediterranean region, Southeast Asia reported on par with estimated global averages. Half a million MDR-tuberculosis cases estimated to have emerged in 2006, 50% were in India and China alone, and 27 countries account for 86% of the world's MDR-tuberculosis burden. Countries in the Americas, western and central Europe and Africa reported the lowest prevalence of MDR tuberculosis[29].

Global estimates of MDR/TB

The total number of MDR-TB cases estimated to have occurred in 2006 among newly diagnosed TB cases was 285,718 (95% CLs, 256,072-399,224), or 3.1% (95% CLs, 2.9-4.3) of the total number of new TB cases estimated in 2006 in the 175 countries (9,123,922). The total number of MDR-TB cases among previously treated cases was estimated to be 203,230 (95% CLs, 172,935-242,177) or 19.3% (95% CLs, 18.2-21.3) of the estimated number of previously treated cases in 2006 in the 175 countries (1,052,145).The global estimated number of incident MDR-TB cases in 2006 is 489,139 (95% CLs, 455,093- 614,215) which is 4.8% (95% CLs, 4.6-6.0) of the total number of estimated incident TB cases in 2006 in 185 countries (10,229,315). Two high TB burden countries, China and India, are estimated to have 240,680 cases (95% CLs, 177,608-307,286) which together account for 50% of all estimated incident cases of MDR-TB[28].

More recently, the emergence of extensively drug resistant tuberculosis (XDR-TB), defined as TB resistant to Isoniazid, Rifampicin, quinolones and at least one of three injectable second line drugs (Kanamycin, Capreomycin, or Amikacin), in every region of the world has raised further alarms about the future of TB control. A review of global DST data conducted by researchers at the CDC found 347 isolates of XDR-TB worldwide, accounting for 2% of all TB isolates surveyed and 15% of MDR-TB isolates; data from African and Asian countries, other than South Korea, were notably lacking[30]. In early 2005, the first reports emerged of an outbreak of XDR-TB at a hospital in rural KwaZulu Natal, South Africa, confirming fears about the rise of drug resistant TB in high HIV prevalence settings[31]. The study showed that of 1539 individuals tested for tuberculosis from January 2005 till March 2006, 542 had atleast one culture that was positive for M. tuberculosis. Of these 542 patients with confirmed tuberculosis, 53 had XDR tuberculosis. The median time of death from sputum collection was 16 days (range 2-210 days) for 52 of 53 who died. In South Africa, Tomsk Oblast (Russian Federations), and Estonia-all countries with high burden of tuberculosis-5.7%, 6.6% and 23.7% of all MDR TB cases were XDR, respectively[8]. There is tremendous concern among public health practitioners that the rise of drug resistant tuberculosis will undermine the success of extent TB DOTS programs and worldwide TB control.

Table 1: Estimated numbers and proportions of MDR-TB among all TB cases by epidemiological region[28]

Regions	No. of All TB cases	No. of MDR TB cases	Low 95% CL	High 95% CL	%MDR TB	Low 95% CL	High 95% CL
Established Market Economies	105,795	1,317	1,147	1,557	1.2	1.1	1.5
Central Europe	50,502	1,201	623	3,694	2.4	1.3	7.2
Eastern Europe	416,316	80,057	71,893	97,623	19.2	18.0	22.2
Latin America	349,278	12,070	10,523	15,526	3.5	3.0	4.4
Eastern Mediterranean Region	601,225	25,475	15,737	73,132	4.2	2.6	11.9
Africa low HIV incidence	375,801	8,415	6,889	18,758	2.2	1.9	5.0
Africa high HIV incidence	2,656,422	58,296	48,718	118,506	2.2	1.9	4.5
South-east Asia	3,464,313	149,615	114,780	217,921	4.3	3.5	6.2
Western Pacific Region	2,173,333	152,694	119,886	188,014	7.0	6.1	8.1
Surveyed countries	7,953,603	408,325	361,264	464,069	5.1	4.7	5.7
Non surveyed countries	2,239,383	80,814	71,684	188,605	3.6	3.2	8.4
All countries (n=185)	**10,192,986**	**489,139**	**455,093**	**614,215**	**4.8**	**4.6**	**6.0**

The ability of DOTS programs to reduce transmission and incidence of both drug susceptible and drug-resistant tuberculosis is debatable; while some studies have shown successful reduction of drug resistance under the WHO strategy[32], others have demonstrated an "amplifier effect" of increasing drug resistance under DOTS-prescribed short-course chemotherapy[12]. One study of patients receiving short course chemotherapy in a penitentiary hospital in Siberia found that over 3% of patients completing treatment, and over twenty percent of patients who began treatment with an isolate resistant to three first-line drugs, had amplified resistance over the course of therapy. Large scale epidemiological data is presently lacking, but mathematical models have suggested that MDR-TB hotspots could evolve in areas with successful DOTS programs due to the amplifier effect[33]. Treatment of multidrug-resistant tuberculosis with second line drugs is much more expensive and requires a longer duration of therapy. As such, it became a contentious public health issue in the past decade, pitting moral and cost-effectiveness arguments against each other in debates about global health resource allocation[34]. Prior to 1999, the prices of second line drugs were exorbitantly high and no global mechanism existed for coordinating supply, negotiating drug prices, financing programs, setting treatment guidelines and standards, and overseeing program performance[35]. In 1999, the WHO and its partners launched a "DOTS-Plus for MDR-TB" initiative, followed by the "Green Light Committee" (GLC) a year later[36]. Together, these bodies have increased access to second line drugs in resource poor settings and ensured that treatment of MDR-TB supplements, rather than detract from, the success and resources of existing TB DOTS programs. Despite the success that the DOTS Plus initiative and GLC have had in scaling up MDR-TB treatment in resource poor countries, only 10,000 patients, or less than 5% of the world's total cases, are currently receiving second line drugs (SLD) through this mechanism[26]. The overwhelming majority of patients afflicted with MDR-TB in developing countries remain without access to second line drugs.

XDR-TB is more expensive and difficult to treat than MDR-TB and outcomes for patients are much worse, therefore understanding the magnitude and distribution of XDR-TB is important. Despite limitations in the quality assurance applied to laboratory testing, data from this report indicate that XDR-TB is widespread with 45 countries having reported at least one case. The high proportion of XDR-TB among MDR-TB as well as the large overall burden suggests a significant problem within the countries of the former Soviet Union. Japan, and the Republic of Korea in a previous study, has also shown a high proportion of XDR-TB among MDR. South Africa reported a moderate proportion of XDR-TB among MDR-TB cases; however, the underlying burden of MDR-TB is considerable and 44% of TB patients are estimated to be co infected with HIV. Few representative data from Africa are available with the exception of Rwanda and preliminary data from Tanzania, which showed no XDR-TB and very little second line resistance among MDR-TB cases suggesting that second-line anti-TB drugs have not been widely used in these two countries; however, risk populations should continue to be monitored. XDR-TB is likely to emerge where second-line anti-TB drugs are widely and inappropriately used; however transmission is not limited to these settings. Data were largely reported from high income countries or with the assistance of a Supranational Laboratory, indicating that countries require strengthened capacity to monitor second line resistance if we are to develop an accurate understanding of the global magnitude and distribution[28].

MDR TB in South East Asia

Six countries reported data from the South East Asia region. Of the six countries, including four settings in India, the median number of new cases tested was 547, and ranged from 101 in Mimika district in the Papua province of Indonesia, to 1571 new cases tested in Gujarat, India. The median number of previously treated cases tested was 162. MDR-TB among new cases ranged from 0.2 %(95% CLs, 0.0-1.0) in Sri Lanka, and 0.7% (95% CLs, 0.1-2.5) in Mayhurbhanj District, Orissa State, India to 4.0% (95% CLs, 2.6-5.7) in Myanmar. India, Nepal and Myanmar showed similar proportions of resistance among retreatment cases. Sri Lanka, showed no resistance and Thailand showed 34.5% (95% CLs, 27.9-41.7) MDR among previously treated cases[28].

The new survey data available from Sri Lanka are showing exceptionally low proportions of resistance. While these data have not yet been fully quality assured, other programmatic indicators support this estimate. All treatment failures cases receive culture and DST and identified MDR-TB cases are managed by the public sector. Sri Lanka is the only country in the region routinely reporting MDR-TB cases. The success rate among MDR-TB cases is not known, but the country has plans to submit an application to the GLC. Nepal and Thailand are the only two countries reporting trend data in this report. The proportion of MDR-TB among new cases in Nepal has fluctuated from a little over 1.0% to 3.0% in the four surveys that have been conducted since 1996 making trends difficult to interpret. The current estimate is 2.9% (95% CLs, 1.8-4.3) among new cases and 11.7% (95% CLs, 7.2-17.7) among retreatment cases.

Nepal has had a well functioning TB control programme for over a decade and both case detection and treatment success remain high. Nepal has proven to be the leader in MDR-TB control in the region establishing the first MDR-TB control programme in the public sector and expanding it's coverage to 100% of the country by the end of 2006. Currently there is one MDR-TB treatment centre and at least three to four sub-centres in all the five regions of the country. Cure rates among registered MDR-TB cases for whom treatment outcomes are available are 75%. Like other countries in the region the ability to expand MDR-TB services has been limited by laboratory capacity however there are plans in place to expand the culture network.

The South East Asia region is home to four high burden countries. Though resistance in the region is moderate the overall burden of MDR-TB is considerable. Important progress has been made throughout the region in initiating plans for MDR-TB treatment and almost all countries in the region have GLC applications approved or in the pipeline. However, with the exception of Thailand all countries have identified laboratory capacity as their primary bottleneck to scaling up diagnosis and treatment to reach the targets outlines in the Global Plan to Stop TB, 2006- 2015. In addition many countries in the region have growing private sectors that are currently managing most of the MDR-TB cases in the region, and second line drugs are widely available through the private sector. Coordinated efforts on behalf of NTPs as well as partners will be required in order to solve the laboratory capacity shortage in the region[28].

Risk factors of MDR

Genetic factors

Though there is some evidence to postulate host genetic predisposition as the basis for the development of MDRTB[37,38,39] the accumulation of changes in the genomic content, occurring through gene acquisition and loss is the major underlying event in the emergence of fit and successful strain variants in the *M. tuberculosis* complex[40]. Spontaneous chromosomally borne mutations occurring in *M. tuberculosis* at a predictable rate are thought to confer resistance to anti- TB drugs[41,42].

MDR TB and health service

Factors related to previous anti tuberculosis treatment

Incomplete and inadequate treatment

A review of the published literature Sharma and Mohan[42] strongly suggests that the most powerful predictor of the presence of MDR-TB is a history of treatment of TB, though some individuals who did not have previous TB treatment can be infected by MDR-TB. Many new cases of MDR-TB are created each year by physician's errors (drugs, dosing intervals, duration). Professor Michael Iseman (1993) the US "guru" of MDR-TB, has shown that two to four errors are needed to turn a fully susceptible organism in to a case of MDR-TB[43]. MDR-TB develops due to error in TB management such as the use of single drug to treat TB, the addition of a single drug to a failing regimen, the failure to identify pre-existing resistance, the initiation of an inadequate regimen using first line anti tubercular drugs and variations in bioavailability of anti-TB drugs predispose the patient to the development of MDR-TB[42]. Shortage of drugs has been one of the most common reasons for the inadequacy of the initial anti-TB regimen, especially in resource poor settings[44]. Other major issues significantly contributing to the higher complexity of the treatment of MDR-TB is the increased cost of treatment.

Inadequate treatment adherence

Non- adherence to prescribed treatment is often underestimated by the physician and is difficult to predict. Certain factors such as psychiatric illness, alcoholism, drug addiction, and homelessness do predict non-adherence to treatment[42]. Poor compliance with treatment is also an important factor in the development of acquired drug resistance. A study conducted in South India[45] observed that only 43% of the patients receiving short course treatment (n=2306) and 35% of those receiving standard chemotherapy (n=1051) completed 80% or more of their treatment. The various reasons for default included travel to different places, symptom relief, adverse drug reactions and inability to afford treatment[46]. MDR-TB requires a two- to four-fold longer period of treatment compared with the drug susceptible TB. Shortest treatment course so far validated for drug susceptible TB is six months long. Most of the problems from which drug resistance originates are related to length of treatment (especially considering tolerability). The longer time that is required to treat MDR-TB clearly implies an additional risk of poor treatment adherence and consequently of treatment failure[47].

Some other factors also play important role in the development of MDR-TB such as poor administrative control on purchase and distribution of the drugs with no proper mechanism on quality control and bioavailability tests[48]. Tuberculosis control program implemented in past has also partially contributed to the development of drug resistance due to poor follow up and infrastructure.

Other factors

A prospective epidemiological case control study was conducted to assess the risk factors of MDR TB in four European countries between 1997 and 2000

with total of 138 cases and 276 controls. Considering the four countries as a whole, the most statistically significant risk factors were as follows: intravenous drug use (OR 4.68); asylum-seeker support (OR 2.55) as income factor; living in a nursing home (OR 2.05); previous tuberculosis (OR 2.03) with pulmonary location; prison (OR 2.02); known tuberculosis contacts (OR 2.01); immuno suppression other than human immunodeficiency virus (HIV) (OR 1.96); acquired immunodeficiency syndrome (AIDS) (OR 1.96); current tuberculosis with pulmonary location (OR 1.77) and health-care worker (OR 1.69)[49].

MDR-TB patients were more likely to have received previous tuberculosis treatment in 22 studies, with a pooled risk estimate of 10 times higher for treated than for new patients. MDR-TB patients were more likely to foreign born in eight studies carried out in western Europe, although one study did not find any association between foreign status and MDR-TB. MDR-TB patients were more likely to be younger than 65 years. MDR-TB patients were more likely to be male. MDR-TB patients were more likely to be HIV positive. MDR-TB was associated with being a prisoner in the five studies which included prisoners(OR1.75; 95% CI 0.90 to 3.40) [50].

Over all multivariate analysis showed that being male, having a history of TB and previous or current treatment for more than 4 weeks, advanced disease with cavitations, and a history of imprisonment remained as highly significant risk factors for single drug resistance and MDR-TB. This study also examined the role of social factors in drug resistance. Smoking was found to be associated with Isoniazid resistance but more evidence is needed to explain this association[51]. In North India, of the risk factors studied for MDR-TB, bacillary load and previous treatment of TB were found significant ($p<0.05$). HIV status, tobacco smoking, excessive alcohol intake, age, sex, education and socio-economic status had no relation to infection with MDR[52].

The variable that was more strongly associated with MDR was previous treatment, as found in many other studies. Previous treatment for tuberculosis has been consistently associated with MDR-TB. The study found a significantly higher proportion of MDR-TB among the age group 45–64 years. This study suggests that patients with alcohol abuse are less likely to have MDR-TB. This is an unexpected finding, since alcoholism has been associated with treatment default and poor treatment outcome among patients with TB in other countries, although some studies could not find a higher risk of MDR-TB in alcoholic patients. The study did not find any association between HIV status and MDR-TB[53].

The association known for centuries between TB and poverty also applies to MDR-TB, a rather significant inverse association between MDR-TB and family income, and between MDR-TB and the number of rooms in the home. The lack of a hydro-sanitary infrastructure (tap water and sewer) in the homes also showed to be associated with MDR-TB. In the research, alcoholism and smoking appeared as risk factors for MDR-TB, whether associated or not. Although the study revealed smoking to be a risk factor for MDR-TB, there is no report about this fact in the literature searched. Yet, there are reports on association between alcoholism and MDR-TB. As for illegal drug use, many authors have investigated this problem but only a few found a significant association with MDR-TB, the present study did not find any association. In agreement with the literature, association was not found in either between MDR-TB and chronic obstructive pulmonary disease, diabetes, or psychiatric diseases[54].

In a study done in Hongkong, among the 322 non-MDR-TB controls, respectively 192 and 130 patients did and did not have a previous history of anti-tuberculosis treatment. Using logistic regression analysis, non-permanent residents (OR 6.85, 95%CI 1.38-34.09), frequent travel (OR 2.48, 95 %CI 1.07-5.74) and younger age were found to be independent predictors of MDR-TB in previously treated patients, whereas living on financial assistance just failed to reach statistical significance (OR 2.75, 95%CI 0.98-7.68, P = 0.05) [55].

Treatment of MDR-TB

Compared with therapy for drug susceptible tuberculosis, treatment of MDR-TB requires a longer duration, is considerably more complicated, expensive, and toxic, and treatment success rates are typically lower. Various treatment strategies have been employed, including the use of standardized treatment regimens based upon representative local susceptibility patterns, empirical treatment based upon previous treatment history and local DST patterns, and individualised treatment designed on the basis of individual DST results[24]. It is recommended that regimens include at least four drugs that are certain, or expected, to be effective and that the duration be a minimum of 18 months beyond sputum conversion. Injectable agents should be used for a minimum of 6 months. Management of patients receiving second line drugs requires fairly intensive monitoring for drug toxicities and treatment failure. While some cohorts have found high rates of treatment interruption due to side effects and toxicities, well designed programs have demonstrated that, in spite of the high frequency of adverse effects, life-threatening adverse events are uncommon and management in resource limited settings can be done successfully. Sputum culture conversion typically occurs between one to two months after the

initiation of therapy, while smear conversion may take longer as it does not distinguish between viable and nonviable organisms[56]. Patients who have persistently positive sputum smears or cultures after three months of therapy with SLD should raise concerns for either poor adherence or improper regimen choice, and further evaluation including DST may be indicated[9].

Treatment outcomes among MDR-TB cases have varied widely; a recent survey of five GLC-approved sites in resource-limited countries found treatment success rates of 70%[57]. A number of factors have been associated with treatment failure and death. In the aforementioned survey of GLC-approved sites in resource-limited countries, treatment success and death rates were 77% and 3.5%, respectively, in new cases and 68.5% and 14% in previously treated cases. Patients infected with HIV have consistently been found to have higher rates of mortality during MDR-TB treatment than HIV uninfected individuals[58]. One case series in South Africa found MDR-TB treatment success rates of 38% in HIV infected individuals, compared with 47% in those who were uninfected[59]. In another cohort in Peru, low baseline haematocrit and body mass index were each independently associated with decreased time to death, while the inclusion of Pyrazinamide and Ethambutol in the regimen (in patients with DST documented susceptible organisms) was independently associated with favourable treatment outcomes[56]. A review of MDR-TB treatment outcomes in Latvia found treatment success of 76% among HIV uninfected patients and of 56% among infected patients; resistance to Ofloxacin was independently associated with a much slower time to culture conversion and an increased risk of poor outcomes[60].

At a programmatic level, the World Health Organization recommends that treatment of multidrug-resistant tuberculosis be based upon principles closely related to those of its general DOTS strategy for TB control: sustained political commitment; a rational case-finding strategy including accurate, timely diagnosis through quality assured culture and DST; appropriate treatment strategies that use second-line drugs under proper case management conditions; uninterrupted supply of quality-assured antituberculosis drugs; standardized recording and reporting system[24]. While these components can be expensive and require substantial investment of human and laboratory resources, the experience from multiple countries is that addressing drug resistant tuberculosis strengthens, rather than detracts from, national tuberculosis programmes. Moreover, data from Peru suggests that treatment of MDR-TB is cost-effective[61]. To date, however, DOTS Plus for MDR has not been implemented on a large scale in Asia, and data on outcomes from the region are limited.

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